Exhibit D

UNITED STATES DISTRICT COURT
SOUTHERN DISTRICT OF WEST VIRGINIA
AT CHARLESTON

IN RE: ETHICON, INC., PELVIC REPAIR SYSTEM PRODUCTS LIABILITY LITIGATION **THIS DOCUMENT RELATES TO WAVE 1**	**Master File No. 2:12-MD-02327** **JOSEPH R. GOODWIN** **U.S. DISTRICT JUDGE**

SUZANNE PARISIAN, M.D.
EXPERT WITNESS REPORT

I. QUALIFICATION AND METHODOLOGY

A. QUALIFICATIONS

1. Since August 1995, I, Suzanne Parisian, M.D., have been President of MD Assist, Inc., a regulatory and medical consulting firm specializing in matters involving the United States Food and Drug Administration's ("FDA") regulation of medical products. I received my Medical Degree (M.D.) from the University of South Florida in 1978, and am Board Certified in Anatomic and Clinical Pathology. I have over thirty-five (35) years of experience in the research and development of medical devices, biopharmaceuticals, and pharmaceuticals. I began my career, as a general physician practitioner, in 1980 and subsequently went into emergency medicine, where I oversaw all medical emergencies at Caldwell Memorial Hospital.

2. From 1991 to 1995, I served as a Commissioned Officer in the United States Public Health Service and achieved the rank of Lt. Commander. I was assigned as a Medical Officer to the FDA's Center for Devices and Radiological Health ("CDRH"). Concurrently, from 1991 to 1995, I was also assigned part-time clinical responsibilities at the Armed Forces Institute of Pathology ("AFIP"), Office of the Medical Examiner for the Armed Forces. At CDRH, from 1991 through March 1993 I was initially a Medical Officer in the Office of Health Affairs ("OHA") a staff office within the FDA to support a non-clinical Director of CDRH. I was primarily engaged in post-market issues for medical devices and protection of the public, including the FDA's oversight of the marketing of medical devices. In OHA I was required by my Supervisor to become versed with the Federal Food Drug and Cosmetic Act and its implementing regulations at FDA.

3. While in OHA, I was a medical officer charged to be responsible for identification and review of public health safety issues, which included voluntary and mandatory medical device reports ("MDRs") review of patient medical records, medical literature, marketing materials, scientific literature and labeling. I was also required to provide FDA's official comments on numerous United Sates and International medical device industry standards as well as guidance documents. Within OHA, I was the primary clinician assigned responsibility to preside over pro hoc meetings for 162 health risk assessments. The assessments were made to advise FDA and CDRH on overall health risk of medical devices' performance issues, help with identification and then communication of public health safety issues, and to make recommendations to FDA regarding subsequent regulatory and medical actions that should be undertaken by FDA, health care providers, users groups and manufacturers in order to help protect the public's welfare. (21 C.F.R. part 7). I was involved in several mandatory medical device recalls and participated with members of FDA's Office of General Consul in development of evidence and obtaining outside medical expert witnesses for a formal regulatory hearing. The mandatory recall actions required me to review company manufacturing documents as well as company

internal documents and employee testimonies. I also served as CDRH's medical expert testifying on behalf of the FDA.

4. In March 1993, the Commissioner of the FDA re-organized CDRH, transferring all medical officers to the Office of Device Evaluation ("ODE"), a pre-market review office for new products. I was one of a handful of medical officers at CDRH and ODE, officially assigned to ODE's Division of Reproductive Abdominal, Ear, Nose and Throat, and Radiology, ("DRAERD"). Within months, I was next made one of two Chief Medical Officers in ODE, now also involved with interacting with other government agencies, industry, the press, health care providers and the public, training ODE clinical personnel and staff regarding the FDA process and requirements, and for a time continuing my role from OHA for health risk assessment process for marketed devices. While in ODE, I performed an additional 100 health risk assessments and trained medical officers as to the procedure for conducting a health risk assessment.

5. ODE, FDA is the Office within CDRH responsible for the premarketing evaluation of product applications submitted by the manufacturer (sponsor) requesting to market new devices within the United States. At ODE, I participated in the review of clinical trial applications and marketing applications including Investigational Device Exemptions (IDE), 510(k)s, Premarket Approval Applications (PMAs), (and for Center for Biologics IND (Investigational New Drug Applications)) and submissions for Combination Products as well as assigned responsibility for training new medical officers and scientific reviewers in application and labeling review at CDRH. I was made an instructor in CDRH's Staff College for instruction of CDRH's reviewers in the design and evaluation of clinical data contained within premarketing applications.

6. Regarding post-market surveillance of marketed products while at the FDA, I participated with FDA's District Offices, Office of General Consul, and the Office of Compliance in the review of manufacturing records, product complaints and adverse event reports obtained by FDA. I was the primary clinician involved in several of FDA's Major Corporate-Wide actions, for which I received various honors for my service at the FDA, including Employee of the Month for the Department of Health and Human Services. I received multiple Unit and Individual Medals from the United States Public Health Service, including two Commendation Medals. I was sent by FDA as its official representative to medical and industry meetings inside and outside the U.S. to help instruct professionals about the regulatory requirements of the FDA and to help FDA monitor the conduct of FDA-regulated manufacturers and distributors for deviations from regulations governing promotional activities. I was also required to provide guidance to health care providers and industry organization as to the FDA's interpretation of food and drug laws as it pertained to FDA-regulated products and the role of manufacturers.

7. One of my assigned responsibilities at the FDA, based on my clinical training and experience, was to review facts contained in product marketing applications, clinical trials, medical literature, reports of post-marketing experience, and available manufacturing documents gathered by the FDA or provided to the FDA by the manufacturer or other regulatory agencies. I was then to use those facts to: 1) make a clinical and regulatory

determination to a reasonable degree of medical and/or regulatory certainty per the requirements of the FDCA and; 2) recommend the next courses of action available to help protect public health. I was also required by the FDA to advise and train other FDA employees regarding the review of facts of a case or issue, the requirements of the Food, Drug and Cosmetic Act, and in making a determination to a reasonable degree of medical and/or regulatory certainty regarding the clinical impact of the agency's actions on the public. This was a process I was trained in and required to perform for the FDA.

8. After leaving FDA in 1995, I founded a consulting firm initially called Medical Device Assistance, Inc. but later changed to 'M.D. Assist, Inc'. I have been president and chief executive officer of that organization since its inception. In this position, I have continued to provide information, advice, and guidance to individuals, trade groups, and professional organizations outside of the FDA regarding preclinical testing, FDA's requirements, Adverse Event Reporting, risk management, promotion and labeling of medical products. FDA convened a panel in 1997 to discuss methods to improve medical device labels, and invited me to participate in its panel of medical device labeling experts convened to provide comments on changes proposed by FDA. I have lectured at industry and medical conferences, seminars, colleges, and for medical societies regarding FDA, premarket clearance and approval, design of clinical trials and post-marketing issues including risk assessment, failure investigation, promotions, claims and product labeling. I am the author of a book titled FDA Inside and Out published in May 2001, which has been used as a college textbook and library reference describing the workings, laws and history of the FDA.

9. During my tenure at the FDA and in my current position as a regulatory consultant, I have reviewed hundreds of marketing applications for safety and efficacy as well as proposed draft labeling and commercial marketing. My medical device experience includes all classes of medical devices: Class I, II and III. In this capacity, I worked with industry scientists and academic clinical investigators for evaluation, marketing and labeling review of new products. I have a broad range of experience that spans multiple medical areas, including women's health, wound healing, gynecology, urology and toxicology to name a few. Both while at the FDA and after leaving the FDA I have been interviewed on several occasions by the press regarding women's health issues and the activities of the FDA. After leaving the FDA, I have presented on women's health issues and the role of the FDA to members of Congress and their staff.

10. As part of twenty years as an FDA Regulatory consultant, physician and former FDA Chief Medical Officer, I have directly assisted industry (manufacturers/Sponsors) with product design and development, identification of predicates, use of voluntary industry standards, FDA's, International Harmonized Guidances for providing adequate documentation to FDA in a pre-marketing submissions(510(k), IDE, PMA and PMA supplement). I have been consulted to create entire FDA submissions (510(k), IDE and PMA) for Sponsors using my own analysis of available medical literature, pre-clinical and clinical data, outcomes, as well as when available post-market information and draft labels and commercial marketing materials. Based on my training and experience at the FDA and as a physician, I have been consulted by Sponsors on different types of preclinical and/clinical testing available for a new medical device, having to review published scientific and

medical literature about the product, help select materials including for implanted products interpreting industry standards and FDA guidances. I have designed protocols for Investigational Device Exemptions (IDE) (*as well as Investigational New Drug Applications- IND), adequate informed consents, investigators' brochures, and suitable methods for data collection, statistical methods to generate scientifically valid endpoints, monitor the various phases of clinical trials to ensure patient safety. I have also been sued to investigate and evaluate adverse events and create periodic reports and communications for FDA. I have been designated as a Sponsor's primary regulatory consultant with FDA on numerous occasions, and have also been used to facilitate meetings between a Sponsor with appropriate members of FDA's ODE staff so that a Sponsor can specifically discuss and negotiate contents of future marketing applications which may be acceptable to FDA.I have provided my expertise to train Sponsors' own regulatory, clinical and marketing staff about the relevant FDA regulatory processes needed for marketing a medical device in the United States including requirements for post-market surveillance, medical device reporting, failure investigation and recordkeeping. I have been utilized by Industry and Sponsors based on my training and experience as a former FDA medical officer as the company's proxy "face of the FDA" (sounding board) to help it better design presentations and interactions with the FDA for both pre-market and post-market issues. I have also been used by Sponsors to help its quality and regulatory staff look for and troubleshoot potential safety issues occurring with its medical devices in terms of my review of adverse events, complaints and the medical literature.

11. My most current curriculum vitae is provided in Attachment "1." I charge $400/hr. per study and $600/hr. for testimony and court.

B. METHODOLOGY

12. I continue to use the same methodology for clinical and regulatory review I was first trained to use while at FDA as a medical officer with consideration of the Federal Food Drug and Cosmetic Act, implementing regulations, global industry standards, in addition to my training as a physician, to analyze the role of Ethicon as a United States medical device manufacturer of a permanently implanted medical device, clinical and scientific information available, quality system regulations applicable to Ethicon's design, testing, risk management, and implementation of manufacturing process controls for its single incision mini sling TVT-SECUR ("TVT-S"). Regarding the regulatory history of Ethicon's commercial (post-market) TVT-S product, I have considered Ethicon's handling of complaints, statistical trending, marketing and communication of risk to health care providers and patients, sales force feedback, post-market surveillance practices and patients' outcome. I have continued to use that same methodology as a regulatory consultant for more than twenty years whether for industry or for litigation support.

13. My regulatory opinions are based on confidential Ethicon documents, employee testimonies, scientific and product design development and testing as well as public information including FDA's documents, global industry standards and issues for similar products. To formulate my expert opinions for TVT-S and actions of Ethicon, based on my training and experience as to the requirements for a United States manufacturer like Ethicon, I have reviewed the medical literature, internal Ethicon documents, employee testimonies, design,

testing and marketing documents for TVT-S as well as similar Ethicon pelvic products, various studies associated with synthetic surgical mesh including mesh implanted in the female pelvis, Ethicon's goals for device characteristics and properties, quality systems and manufacturing documents including Ethicon's internal risk management, device Failure Modes and Effects Analysis (dFMEA) and its interactions with its sales force and marketing to physicians and women. My regulatory opinions will be focused for each plaintiff on the relevant case-specific depositions and her timeframes as to TVT-S implantation and when applicable, explanation, including timing, reports of the operative findings and additional surgery(ies).

14. My opinions are not intended to address medical causation or standard of care in terms of the treating physicians. I have employed reasonable methods and when relevant have also relied on global industry standards, including the Global Harmonization Task Force ("GHTF"), French National Authority for Health ("HAS"), National Institute for Health Care Excellence ("NICE"), International Organization for Standardization ("ISO"), International Electrotechnical Commission ("IEC"), and the Asian Harmonization Working Party ("AHWP"), all of whom are liaison body members of the GHTF. These organizations along with FDA have helped develop a series of inter-related documents and accepted actions for voluntary adoption by an international company like Johnson and Johnson's Ethicon to help harmonize medical device development. In terms of Ethicon's marketing of TVT-S in the United States, I rely on my own experience as an American trained physician and FDA regulatory expert, the FDA's history of TVT-S clearance which permitted commercial marketing. My expert opinions are formulated using the same methodology I first learned to use at the FDA for pre-market and post-market review and it provides the overall support for the expert regulatory opinions that I plan to offer regarding TVT-S.

15. As part of my standard methodology, I have conducted my own review of FDA's database, including the FDA Advisory Committee Transcript for the September 2011 meeting on SUI, and the U.S. medical literature through the National Library of Medicine's database to obtain documents pertaining to the use of the transvaginal mesh (TVM) for treatment of stress urinary incontinence (SUI) as well as for the single incision mini sling and TVT-S. I have reviewed Ethicon and TVT-S and SUI documents available to me within the public database in terms of support for regulatory opinions and my development of a regulatory timeframe for Ethicon's actions for its SUI products that will be related to each plaintiff. The product materials that I have reviewed in this matter are the exact same types of materials that I have been preparing or reviewing to ensure their accuracy, truthfulness, and their entirety during my professional career. Therefore, I am familiar with the types of documents reviewed here and Ethicon's regulatory responsibilities to physicians, consumers, and general public in this case for its commercial TVT-S product.

    a. I have been asked to address the actions of Ethicon in the context of the company's responsibilities as the United States manufacturer of the TVT-SECUR System sold as TVM for SUI. The TVT-SECUR was cleared through a 510(k) (K052401) for marketing on November 28, 2005. It was cleared to be legally marketed in the United States as intended as a sub-urethral sling for the treatment of SUI resulting from urethral hypermobility and/or intrinsic sphincter deficiency.

b. Ethicon initially indicated to FDA in its 510(k) that TVT-S commercial performance was a modification of its TVT slings for SUI and that Ethicon had found it substantially equivalent to Ethicon's GYNECARE Tension Free Vaginal Tape (TVT) System (K974098, K012628-TVT Blue Mesh) and GYNECARE TVT Obturator (TVT-O) System (K033568)(predicates). However, based on the concerns of the consulting Medical Officer and urologist, Dr. Herrera, FDA asked Ethicon in a letter of October 25, 2005 to provide 12 months of clinical data to support the adequate performance of TVT-SECUR as a new SIS mini sling. Ethicon's response was to provide FDA with additional detail on its sheep study and identification of a new predicate Gyne Ideas Mini Tape (K023898) (cleared June 18, 2003 as a mini tape for SUI without a requirement to provide clinical data and follow up). As a result of its response to FDA, Ethicon was able to obtain FDA's clearance of TVT-SECUR on November 28, 2005. Ethicon as part of the FDA's mandatory least burdensome method for reviewers would cite (bridge/reference) the testing information contained in TVT and TVT-O 510(k)s for its Prolene sling, the testing information in Ethicon's Codman Ethiosorb Dura Patch (K991413) (*a neurosurgical Dura Patch made of fleece with absorbable 910/polydioxanone (Vicryl)/PDS material with one side coated with PDS film (polydioxanone) for addition to the ends of the Prolene mini tape.), and the history of Vicryl Suture (N17-482, K946271) and PDS suture (N18-331) for the modified sling ends.

16. During the preparation of this Report, I additionally reviewed, consulted, and relied upon the following categories of information, listed in my reliance list, which include: internal Ethicon documents produced in this litigation; relevant scientific and medical literature; trial and/or deposition transcripts (and exhibits)(documents I located on-line, which include a review of Johnson & Johnson's website; and other relevant websites, including the 510(k) database and MAUDE; and applicable statutes, regulations and guidance documents; premarket notification 510(k) documents; other 510(k) Summaries relevant to the TVT-SECUR product development histories.

17. My expert regulatory opinions utilize the same techniques, processes, methods and types of documentation used by other FDA regulatory experts. My opinions also rely heavily on my training as to FDA's and industry's use of voluntary industry standards for development and support of products for marketing, discussed above. My opinions also rely on my medical and scientific training and post-market experience at FDA with health risk assessment and evaluation, voluntary and mandatory recalls, toxicology, biomaterials safety notification and my professional experience, permits me to incorporate the health risk (clinical impact) of Ethicon's regulatory actions with TVT-SECUR on the public. This impact on the public would also be seen in terms of Ethicon's adherence (or lack of adherence) to various industry standards and Ethicon documents regarding FDA's minimum requirements and its internal operating procedures for current good manufacturing practices of the quality systems regulations (GMP/QSR) in its manufacturing, post-market monitoring, failure investigation, complaint handling, corrective and preventive actions (CAPA) and voluntary actions to protect women. Just as I was first requested to do at the FDA and I did also for

manufacturers after FDA, I review each document or testimony within a regulatory framework to make a determination if it is an example of acceptable or not acceptable behavior in terms of the Food Drug and Cosmetic Act and specific implementing regulations for a manufacturer. When also viewed in the medical and scientific context does an action provide evidence of a potential known or knowable risk for Ethicon in term of patient safety. This two-prone evaluation is no different from what I have been doing for the past twenty-four (24) years. In essence, I reviewed the background research, information, formulated theories, tested my theories against the information that I reviewed here while heavily relying on the regulations and through my knowledge, experience, training at FDA, and regulatory expertise coherently communicated my conclusions in this Report.

18. Over the course of my career, I have been an integral member as a regulatory consultant for multiple companies and review teams, where we determined whether the products would be sufficient to meet FDA's regulatory requirements and global industry standards. As part of this analysis, I would consider whether additional studies/testing was required, and, if additional studies/testing was required, what types of studies/testing were needed. Additionally, I determined whether the proposed device label was adequate and all-encompassing according to the various industry and regulatory standards and my training and experience. For example, in my role as the Medical Officer in OHA, I was required to provide FDA's official comments and participate with various International and national industry groups to help develop industry standards' for medical devices. Since leaving the FDA there were many years when I continued to be a regulatory and medical expert on industry standard committees involved with design, development and critique of voluntary medical device industry standards. I have often been asked to evaluate the types of proposed testing/studies for a manufacturer as related to industry standards for manufacturing and clinical trials needed to obtain patient data and update labeling and marketing and training even when clinical studies were not required under FDA's guidelines to obtain 510(k) clearance. I have utilized clinical trials and studies (clinical data) to inform companies and physicians about the risk/benefit ratio of a particular product or types of products, which assisted them in the creation of IFUs , training and marketing materials, which had to be consistent with both the potential risks and benefits of a new device or product and FDA's intended use. I have presented on US medical devices to foreign regulatory agencies as well as foreign medical organizations as to how products were evaluated in the United States, the use of the product in patients, labeling requirements for the FDA, as well as for helping industry obtain reimbursement from the foreign regulatory agency. I also had to have a working familiarity with United States and International standards and requirements to help a Sponsor harmonize its products for marketing both in and outside the United States.

19. My analysis in evaluating the TVT-S factors in a multitude of sources in the context of the FDA requirements and are not different than those employed throughout my career in medical product research and development.

20. In addition, I was directly involved in the writing and review of Dear Health Care Provider Letters, FDA Safety Alerts, Public Health Notifications as well as Briefing materials and presentations to the FDA Advisory Committee Panels to discuss safety issues and FDA's

concerns for products. I have worked on labeling and marketing materials for companies, informed consent, training materials, investigator brochures and patient marketing. I was first instructed on the methods of regulatory evaluation to ascertain the adequacy of labeling and warnings for CDRH's Office of Compliance. The review would include the adequacy of labels (including IFU and physician training manual) in terms of the regulations including, advertising and marketing when intended for health care professionals,(including adequacy of prescription labels), as well as for patients, Direct-to-Consumer marketing to the public and labeling and Instructions for Use (IFU) for the home health care environment while at OHA. I was also required to review for FDA the medical and scientific literature, patient case reports and adverse events, and medical device reports (MDRs), and to identify off-label and/or unsupported claims and marketing by industry and provide recommendations to FDA for actions by the Agency and changes to labels, marketing and warnings. I continue to do all these same functions today both for industry and litigation support.

21. I have presented at industry meetings about the FDA and its processes and requirements. I have trained college students, including engineers, going into the medical device industry. I have trained medical students, residents and physicians about the regulatory process, clinical trials, adverse event reporting and risk assessment. I am the identified resource for the Arizona Medical Association to interact with the media about issues dealing with FDA. For the Regulatory Affairs Professionals (RAPS), I was an instructor in its online course on FDA and Medical Devices. Moreover, I have worked with companies and their adverse event evaluation staff to identify safety signals in complaint files and manufacturing records and discussed how to best deal with post-market safety issues and interaction with the FDA, physicians and the public.

22. Specifically for Johnson & Johnson, I was invited to present at one of its National Sales Meetings about the FDA process and instruct its employees on how to investigate and report safety issues (adverse event reports) for drugs and devices.

23. Finally, for clarification, I intend to offer no unsupported subjective opinions regarding Ethicon's intent or state of mind. I also intend to offer no case specific medical causation or medical standard of care opinions regarding a particular plaintiff.

II. OVERVIEW OF REGULATORY PROCESS AS BASES FOR OPINIONS

24. The FDA was given responsibility to be the gatekeeper for the public for new medical devices entering the United States market by Congress through its passage of the Medical

Device Amendments (MDA) of 1976 to the Federal Food Drug and Cosmetic Act. As the assigned gatekeeper for the American public, the FDA was required to establish methods to regulate medical devices similar to human pharmaceutical drugs with both pre-market review phase and post-market requirements for the sponsor with the commercial product. The FDA was required to establish methods for conducting pre-market review and show acceptance that a product met a certain regulatory standard to start marketing in the United States. The FDA's role was also to establish minimal standards for Good Manufacturing Practices (GMP) for industry as well as the marketing claims that could be made for a new product in the United States based on scientific information provided. GMP requirements of 21 C.F.R. § 820 was later amended by the Safe Medical Device Amendments (SMDA) to include new emphasis on industry's use of pre-market design controls and risk management, and GMP is now called Quality System Regulations (QSR) (21 C.F.R. § 820).

25. Most new medical devices, not specifically exempted from FDA's pre-market review, usually enter the market by either obtaining a 510(k) clearance or through Premarket Application Approval (PMA). Ethicon was able to legally market the TVT-SECUR System in the United States based on its successful submission of Ethicon's 510(k) application that was cleared by the FDA. The new device itself was not required to be submitted to FDA, nor did FDA conduct any physical laboratory or patient testing or examine manufacturing procedures. Ethicon was the knowledgeable expert for the product. Ethicon's submission claimed to FDA's reviewers that Ethicon had determined that its new proposed device described in its 510(k) submission as the TVT-SECUR was substantially equivalent to other already cleared and marketed Ethicon devices and raised no new issues of safety and effectiveness that had not been adequately addressed.

26. I will further describe the TVT-SECUR 510(k) clearance process and the history of Ethicon's interactions with FDA pre-market and post-market as well as physicians. Based on the information reviewed, Ethicon did not take the reasonable care of a United States medical device manufacturer to ensure that TVT-SECUR complied with the Federal Food Drug and Cosmetic Act. Ethicon had not adequately designed and marketed a safe and effective permanently implanted TVT-SECUR product as a sub-urethral TVM sling for SUI. Ethicon did not provide adequate risk information to FDA, physicians or to women. Ethicon did not determine and adequately describe safety and efficacy issues it knew were occurring for its TVT-SECUR to FDA and even more importantly it failed to describe the risks to physicians and women. Ethicon also engaged in violative promotion activities with the device for SUI. Ethicon's actions with the TVT-SECUR misbranded the product when it failed to monitor commercial performance to update physicians with risk information. Also Ethicon's marketing implied to physicians that its 510(k) cleared TVT-SECUR had been approved and found to be 'safe and effective.' This representation by Ethicon grossly overstated the oversight role of the FDA in Ethicon's clearance to market TVT-SECUR.

A. THE § 510(K) CLEARANCE PROCESS VERSUS PREMARKET APPLICATION APPROVAL (PMA)

27. Medical devices were subjected to regulation after commercial use (post-market) under the Federal Food, Drug, and Cosmetic Act (FDCA or 'Act') of 1938. However, until 1976, there

were no requirements that devices be reviewed or approved by FDA "before they were actually commercially distributed" (i.e. pre-market) in the U.S. Prior to 1976, device regulation was defined only by the FDCA's misbranding and adulteration provisions, similar to the way foods and cosmetics are still regulated, and the agency's regulation of medical devices was 'after the fact' or after a safety issue occurred. FDA had been given no legal authority to keep unsafe medical devices from entering U.S. commerce prior to 1976. In some rare instances, FDA was able to provide oversight for selected new medical devices through premarket review authority by using the drug regulations as 'new drugs'. For example, Johnson & Johnson's PROLENE suture was originally regulated as a new drug through drug regulations requiring FDA pre-market approval of a New Drug Application. (NDA) The situation for medical devices changed when Congress enacted the Medical Device Amendments (MDA) of 1976 to the Food, Drug and Cosmetic Act (FDCA), which finally gave FDA the authority to require a pre-market review for medical devices before entering the market. Medical devices like Johnson & Johnson's Prolene suture were then transitioned to regulation as medical devices, and called Pre-Amendment transitional devices. The approved NDA for Prolene suture was changed (transitioned) to an approved Premarket Approval Application (PMA).[1]

28. The FDA implemented a risk based system for classification of medical devices starting in 1976. This system classifies medical devices into one of three regulatory classes based on the level of risk associated with the device for the public and the amount of manufacturing control necessary to ensure that the device is safe and effective for its intended use.[2] Devices which appear to pose the lowest risk for the public and require the least amount of manufacturing control, are placed as a Class I device and receive the least regulatory oversight and are applicable to general manufacturing controls. Class II devices pose greater risks for the public, require increased controls in terms of manufacturing, as well as monitoring and labeling. Class III devices are considered the highest risk or require the greatest amount of FDA oversight before marketing. Ethicon's TVT-SECUR was cleared by a 510(k) as a Class II device. FDA is now proposing to reclassify the TVM POP devices into Class III to require PMA approval before marketing based on risks to the public.

> **Class I**- General controls: Regulates devices for which controls other than special controls or premarket approval are sufficient to assure safety and effectiveness. Such controls include regulations that (1) prohibit adulterated or misbranded devices; (2) require domestic device manufacturers, initial distributors, and distributors to register their establishments and list their devices; (3) grant FDA authority to ban certain devices; (4) provide for notification of risks and repair, replacement, or refund; (5) restrict the sale, distribution, or use of certain devices; and (6) cover Good Manufacturing Practices (GMP) or Quality Systems Regulations (QSR), records, reports, and inspections. These minimum requirements apply to all classes of FDA-regulated devices.

[1] Ethicon's Prolene suture with the approved PMA was later reclassified (down-classified) by FDA to class II so that it could be marketed by clearance of a 510(k).
[2] 21 C.F.R. § 860.3.

> **Class II-** Special controls: Regulates devices for which general controls alone are not sufficient to provide reasonable assurance of safety and effectiveness and for which sufficient information exists to be able to establish special controls that are necessary to provide this assurance.
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> **Class III-** Premarket Approval: Regulates devices for which insufficient information exists to determine the general controls and special controls that will provide reasonable assurance of safety and effectiveness. Generally, class III devices are those represented to be life supporting or sustaining, those implanted in the body, or those presenting potential unreasonable risk of illness or injury, or those devices were there is insufficient information for FDA to determine the potential safety and effectiveness.

29. Class I and II devices are often brought to the United States market through a premarket notification process, called a 510(k) application. Over time and to help reduce agency expenditure of resources, FDA has exempted most Class I and many Class II devices from a requirement for obtaining 510(k) clearance by FDA before start of marketing, with general and specific controls still applicable for the sponsor of the product. The riskiest devices, devices with the least scientific information known about performance and/or manufacturing controls necessary to ensure they are safe and effective, or 'pre-Amendments' devices on the market before 1976 earmarked for later review by FDA, are devices requiring the greatest FDA resources and oversight by FDA and industry and are classified as 'Class III'.

30. Generally, Class III devices cannot be brought to market until a sponsor legally completes a successful Premarket Approval ("PMA") process. These Class III devices are to be approved by FDA as supporting safety and efficacy based on scientific evidence for specific indications. The PMA approval process, unlike the standard 510(k) clearance, includes FDA's approval of a sponsor's proposed manufacturing controls, a clinical investigation with clinical data able to support the proposed success criteria, the sponsor providing its draft labeling and post-marketing requirements (21 C.F.R. § 814). PMA approval usually requires submission of a series of clinical trials with patient data obtained in the United States under a FDA approved Investigational Device Exemption protocol (IDEs) (21 C.F.R. §812). The IDE also has a requirement for the participant in the trial to give adequate written informed consent to participate (21 C.F.R. § 50) and Institutional Review Board (IRB) oversight, monitoring and reporting (21 C.F.R. § 56). The IDE process was established by Congress and FDA to ensure that medical device research is conducted ethically and that patients are informed of the risk and willing agree to participate.

31. In contrast to the PMA which is required for a sponsor to obtain FDA's approval of a new device or technology or claim, the 510(k) sponsor must provide an application that can indirectly support safety and efficacy for an intended use. A 510(k) application is a premarket submission (paper application) made to the FDA in which a sponsor (the expert for the product) attempts to support that its new proposed device it intends to manufacture when it is commercially marketed for an intended use is substantially equivalent (SE) to an already legally marketed device (commonly referred to as a "predicate" device) sold for the

same intended use.[3] The sponsor of the new proposed product, based on successful support of substantial equivalence for same intended use to the FDA, within the 510(k) process can rely (bridge) on the history of safety and efficacy of it already cleared commercial marketed device (predicate). The 510(k) process results in a FDA marketing 'clearance' not a FDA 'approval' for a sponsor to start marketing a new product. The FDA's 510(k) review is required, by regulation, to be completed by the assigned FDA Office of Device Evaluation (ODE) reviewer within 90 working days.[4] The FDA's ODE (Pre-market) review will focuses on the sponsor's information in the 510(k) as to whether the new device shares the same intended use, design, materials, or other characteristics of the predicate device. The FDA reviewer, who is usually a scientist but not clinically trained, is to be adequately informed by the submitting sponsor, viewed as the expert in the product, if there are new issues of safety and effectiveness which still need to be addressed by the sponsor for the new device when compared to the marketed predicates. As industry is aware, the 510(k) process relies on a FDA Reviewer's completion of a 510(k) Substantial Equivalence Decision-Making Tree Flowsheet which is kept as part of the official FDA record. Based on the information inserted into the decision tree by the reviewer, the sponsor may be requested to provide additional information (AI) or address new issues of safety and effectiveness now present with the predicates cited.

32. The FDA's ODE reviewers within limits can request additional information (AI) for completion of a 510(k) from the sponsor to address substantial equivalence of the new and predicate devices, and may place the application on hold. However, the number of times that new information is requested is limited internally for FDA's reviewers and the testing requested must be able to be justifiable in terms of testing required of other sponsors for similar products. (i.e. level playing field). Therefore, there are limitations as to what the FDA reviewer is permitted to request from a sponsor like Ethicon for consideration of clearance of a TVT-SECUR 510(k). Also, there is an emphasis at CDRH ODE in completing 510(k)s efficiently and making a decision about ability to clear (or not clear) within 90 working days. Each review round that a reviewer holds a 510(k) for obtaining additional information is recorded and will be reviewed by FDA's upper management annually in terms of each review branch, the Branch Chief and individual reviewer. Delay in efficient handling of assigned 510(k)s will directly impact the ODE Branch Chief and employee's annual work review history and future job assignments and funds. A report on ODE's efficiency including time for completion of submitted 510(k)s is also presented to Congress each year as support for efficiency and will directly impact the annual payment of Medical Device User Fees by industry. MDUFA fees are paid to FDA for CDRH use based on support of agency 'efficiency'.

33. Clinical trials are generally not required to substantiate the safety or effectiveness of a device submitted pursuant to the 510(k) process. [5] However, there are times when preclinical testing, including laboratory and animal studies, and/or clinical data (human data) are

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[3] *See* Premarket Notification, U.S. Food and Drug Administration, available at http://www.fda.gov/MedicalDevices/DeviceRegulationandGuidance/HowtoMarketYourDevice/PremarketSubmissions/PremarketNotification510k/default.htm] (last visited July 14, 2015).

[4] *Id.*

[5] *Id.*

required from a sponsor to be able to address for the FDA potential new issues of safety and effectiveness for its device design, performance or intended use. Clinical trials are also used by industry to investigate and update its products ethically in American patients. For a 510(k), as with a PMA, for a sponsor to obtain clinical data legally with United States patient requires the clinical study to be conducted under an IDE, with the patient receiving and signing an adequate informed consent and Institutional Review Board oversight, monitoring and reporting (21 C.F.R. § 50; 21 C.F.R. §56).

1. Investigational Device Exemption (IDE) – 21 CFR §812

34. A Sponsor who knows a new device is not "substantially equivalent" to a pre-Amendment device or who is not sure if a device is "substantially equivalent" without conducting a clinical investigation (in patients) must obtain a FDA approved IDE to ethically conduct the clinical investigation in the United States. After collecting clinical data, a sponsor who desires to market a device must either submit a premarket notification (510(k)) or premarket approval application[6] to FDA. A premarket notification may be submitted if the sponsor believes the data supports a finding of substantial equivalence. There is nothing that prevents a sponsor from using the IDE to perform clinical trials to obtain patient data for a cleared commercial device.

35. The Investigational Device Exemption (IDE) was reportedly designed by Congress to ensure that valid scientific information (21 C.F.R. § 860.7) can be "legally and ethically" obtained by a sponsor while ensuring public safety. An IDE (21 C.F.R. Part 812) requires that a product's sponsor first obtain FDA's approval of an investigation device exemption (IDE) for a significant risk investigation request prior to beginning distribution of an investigational product for a human trial in the United States. The purpose of clinical investigations done for FDA with an IDE is that a sponsor may eventually submit a marketing application to FDA for support of premarketing clearance or approval of a new device and/or of a marketed device's new indications or claims. A clinical investigation involving the implantation of a permanently implanted device, such surgical mesh as a sub-urethral sling for stress urinary incontinence (SUI), is a significant risk study. In a human population in the United States it would constitute a significant risk investigation and is required to be legally done by the sponsor first obtaining FDA's approval of an IDE.

36. The Investigational Device Exemption (IDE) technically "exempts" an investigational device from certain requirements of the FDCA in order to allow for legal interstate transport and distribution of a product that is not yet in full compliance with the FDCA. The IDE exempts the 'investigational' device from fulfilling the FDCA's requirements for misbranding, premarket notification, and certain good manufacturing practices. To help

[66] Product Development Protocol or 'PDP' is another less-frequently used pre-market route for obtaining FDA's approval for marketing. The PDP entails a series of pre-agreed (between the sponsor and FDA) upon development and testing protocol and description of the outcomes capable of supporting the ability of FDA to approve a new product for marketing. The PDP is called "completed" when all evidence of success for pre-agreed upon parameters have been met. The PDP is also referred to as approved when the FDA determines the PDP has been completed and the outcome is successful. Both the PMA and PDP are described by 21 C.F.R. § 814. The PDP is used as a less frequent pre-marketing route due to the increased involvement of the FDA in the process and its requiring fulfillment of specific pre-agreed success criteria.

further the development of new medical devices for the public, once an IDE application is submitted to the FDA, the agency has a mandatory 30 days to either approve or deny a requested IDE protocol or the protocol will be automatically approved. There are no fees for industry required for FDA's review of IDEs.

37. IDEs can be 'conditionally approved' with a FDA letter requesting additional information or changes to the proposed protocol or handling of the data. The conditionally approved IDE is able to be started by the sponsor, but the conditions must be met for the IDE. IDEs can also be denied by the FDA, however, the FDA's letter to the sponsor must clearly provide the sponsor with guidance as to why the IDE request was denied and changes necessary to permit the IDE to be approved.

38. Without first obtaining approval of an IDE, a sponsor who begins or encourages clinical investigations in United States patients for significant risk investigations with its product, particularly without obtaining pre-marketing approval or clearance, or to support new performance claims, is in violation of the FDA's laws, a Prohibited Act by the FDCA. By FDCA, a U.S. manufacturer (a sponsor) is held responsible to FDA for maintaining control and accountability of its investigational device (i.e. unapproved or not cleared indication, Class III) and for monitoring the conduct of its investigations and safety of the public.

39. Controls to protect the safety and rights of patients include the sponsor obtaining FDA's approval of a proposed IDE protocol (plan) to ensure the quality of the information developed and safety of the subject and that adequate data will be generated for either clearance or approval. The IDE protocol has pre-established success and failure criteria and a written plan for a specified number of subjects (inclusion and exclusion criteria) and when the protocol will be stopped. Another requirement for an IDE is that the patient as a participant in an IDE study, has treatment converted from a physician's 'patient' to an investigator's 'subject'. Each subject enrolled in a clinical trial under an IDE must be given an opportunity to provide and sign adequate informed consent agreeing to voluntarily participate in the proposed study. The informed consent must include a statement that the proposed product is 'investigational' and safety and effectiveness has not yet been determined. In a Sponsor's clinical investigation, the physician becomes a 'clinical investigator' for the Sponsor, no longer simply treating a patient. In return, the Sponsor is required to provide adequate risk information to the investigator. The clinical investigators must sign an agreement to participate in a clinical study for the Sponsor, and will adhere to the approved protocol. Finally, as an extension of the FDA's process for ensuring patient safety, there is required recordkeeping, periodic reporting, oversight and monitoring of the clinical investigation progress by an Institutional Review Board (IRB). An approved IDE protocol will require periodic reporting to both FDA and the IRB by the investigators and Sponsor and there will be required follow-up documentation for the outcome of each subject enrolled. Ethicon as a major medical device manufacturer is aware of and has fulfilled IDE requirements for conducting some of its research in the United States. Physicians and patient must be advised by a Sponsor when they are both participating in a Sponsor's product development.[7] The Sponsor is the entity which will profit from the research conducted in humans with its device.

40. When clinical data is obtained for a significant risk device in United States patients, particularly permanently implanted devices and provided to the FDA in pre-marketing applications such as 510(k)s, it was required to have been obtained ethically under an approved IDE. However, as Ethicon would be aware, members of FDA's ODE pre-market staff, particularly members with surgical devices, are to complete application review within the 90- days timeframe. This group of reviewers have been openly criticized for not following-up on how certain clinical data was obtained by a sponsor using United States patients without evidence of an approved IDE. It could be a role of ODE reviewers, a role usually not pursued, to identify if a Sponsor had encouraged or promoted physicians or had any involvement using their own patient populations 'off label' to obtain clinical data for the Sponsor outside a FDA approved IDE. FDA will always accept human safety information, but efficacy information with United States patients is to have been obtained using the IDE process. FDA has noted shortcomings, often based on limited resources, in its premarket review, postmarket surveillance and oversight of medical device manufacturers.[8]

41. Any action by a Sponsor which encouraged, promoted off-label – investigational- (not cleared/not approved-Class III) use of a new product or an already cleared product for a new indication or claims is not in compliance with the Act and, whether there is official regulatory action taken by FDA or not, it is still an example of misbranding and marketing of an adulterated device without an IDE and a violation of the premarket clearance/approval process.

2. Safe Medical Device Amendment of 1990 (SMDA)

42. After a review of FDA's classification actions by Congress, which occurred during the mid-1980s and its detection of FDA's overwhelming reliance on the 510(k) pre-market notification process rather than the requirement for the more scientifically rigorous premarket approval applications (PMA)s and/or FDA's issuance of Performance Standards, Congress opted to accept FDA actions as valid and passed the Safe Medical Devices Act of 1990 (SMDA). Congressman Henry Waxman and Senator Edward Kennedy were the chairperson sponsors of the SMDA. It was enacted by President George H. W. Bush on November 28, 1990. At that time, Congress accepted the FDA's assurances that FDA's reliance on premarket notification (510(k)) process as the primary safety and effectiveness screen for new medical devices was valid. Congress however shifted the FDCA's focus away from premarket review by FDA to an increased emphasis on active postmarket oversight strategy for industry (i.e. mandatory adverse event reporting- MDR) for protecting the public's health.

43. The SMDA followed an eight year U.S. Congressional inquiry of the Medical Device Amendments of 1976 and the FDA's reliance on 'substantial equivalence'. The General Accounting Office (GAO) presented exhibits for the legislative review which defined the

[8] GAO testimony before the Subcommittee on Health Committee on Energy and Commerce, House of Representatives Medical Devices: Shortcomings in FDA's Premarket Review, Postmarket Surveillance, and Inspections of Device Manufacturing Establishments. Statement of Marcia Crosse, Director, Health Care June 18, 2009.

vulnerabilities of the 510(k) notification process. In that GAO review, it was identified that some qualified medical devices were disallowed testing in some instances, inadequately tested in a clinical setting and others deficient in adverse data collection and oversight by industry and FDA. The US Congressional review concluded that medical devices would require actual device experience in a clinical setting and sufficient reporting of adverse event data. There was a greater emphasis by SMDA placed on the post-marketing monitoring and submission of MDRs as well as improved design and risk management by industry instead of the prior emphasis on FDA premarket review.

44. After SMDA, a predicate device could now be a device that could demonstrate that it had been legally marketed in the U.S. prior to 1976 for the same 'intended use' and for which FDA had not identified a safety and effectiveness issue. With rare exceptions, all pre-1976 devices (i.e. pre-Amendments) on the US market before 1976 were automatically grandfathered as safe and effective for the same intended use for which it was sold prior to MDA. All subsequent premarket notification applications or 510(k)s must include a distinct Summary of Safety & Effectiveness (SSE) section written by the sponsor (and not the FDA), that described the rationale for substantial equivalence or marketing clearance. That information is then published on the FDA's 510(k) website of cleared devices.

3. Substantial Equivalence for the Same Intended Use to Support 510(k) Clearance

45. At time of 510(k) review, if the FDA determined based on the sponsors submission that a device was substantially equivalent (SE) to a predicate device(s) for the same intended use, the manufacturer will be given "clearance" to begin to market a product in the United States. However, by SMDA the sponsor was to remain the knowledgeable expert in submission of the 510(k) description for FDA and the performance and risks of the device and similar devices in terms of adequate design, risk management, testing and subsequent post-market monitoring and performance. Sales of the new product in the United States can begin when a sponsor receives a 510(k) clearance letter.[9] If the FDA cannot conclude based on the information received in the sponsor's application that the device is substantially equivalent (SE) to any predicate or has a new intended use or raises new issues of safety and effectiveness that have not been addressed, the Sponsor receives a not substantially equivalent letter (NSE), with the new device classified as 'Class III'. As an NSE device the Sponsor, to eventually market a Class III device (or cleared device for a new Class III indication), is to proceed through the PMA route (or Product Development Protocol "PDP"). The Class III device (or indication) is required to be first 'approved' by FDA for marketing. The alternative for a NSE Class III product is for the sponsor to identify a different suitable predicate and resubmit a new 510(k). (21 C.F.R. § 814).[10]

4. Medical Device User Fees Based on FDA's Reviewer Time and Use of CDRH's Resources

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[9] *Id.*

[10] *Id.* FDA has established a 'De Novo 510(k)' process for clearance of certain low risk medical devices based on available controls. However, a discussion of De Novo 510(k) is not applicable to TVT-S and TVM products.

46. The PMA process is unquestionably considered to be a more rigorous undertaking than the 510(k) process and as such it requires greater allotment of FDA's resources to complete. The Medical Device User Fee Act (MDUFA) calculates user fees annually for industry to pay based on FDA's reviewer time and Agency resources. The FDA's fee for a Sponsor in 2016 to submit an 'original PMA' for review and approval by FDA is: $261,388; a PMA 180-day supplement has a fee of $39,208; a real-time Supplement has a fee of $18,297; annual report review by FDA has the fee of $9,149; and a 30-day notice for FDA is $4,182. The MUFDA fee for submission and review of a 510(k) is: $5,228 (small business $2,614). There is no MDUFA fee for a sponsor's submission and review of an IDE application which is mandated to be completed by FDA within 30-days or automatically approved. A request for information from the FDA regarding the appropriate regulatory pathway is a called a '513(g)' which has the fee for industry to pay to the FDA of $3,529 (small business $1,765).

47. The PMA process at CDRH is analogous to Center for Drug Evaluation and Research (CDER's) New Drug Application ("NDA") process used for approval to market human pharmaceutical drugs or Center for Biologics Evaluation and Research (CBER's) Biologics License Application ("BLA") process used to license the marketing of New Biologics.[11] Unlike the 510(k) clearance process, the original PMA, NDA, and BLA processes all require a lengthy application process, a series of clinical trials and must demonstrate the product's safety and effectiveness through supplying of valid scientific evidence.[12] Most often, these approval paths require manufacturers to conduct prospective controlled phased clinical trials. These approval applications must be reviewed by FDA's teams of reviewers, and if the Sponsor is successful, will result in FDA's approval (licensing) of a device, drug, or biologic.[13] All subsequent changes to an approved PMA, NDA, or BLA product are then made as PMA, NDA or BLA supplements to the initial application, again with user fees commensurate with the anticipated FDA reviewers' time and agency resources.

48. Manufacturers of marketed devices are also required to get the appropriate clearance or approval to introduce either a device into commercial distribution for the first time or to introduce or reintroduce a device that will be significantly changed or modified to the extent that its safety and effectiveness could be affected. New claims for an already 510(k) "cleared" device, or new indications for an already 510(k) cleared device occurring within labeling and advertising that may potentially alter safety and effectiveness are required also be reviewed and cleared (or approved) by FDA in a premarketing application prior to the start of legal marketing within the U.S. However, the Sponsor of a 510(k) cleared device can immediately update and improve its own label without any requirement for interaction with or approval from the FDA.[14]

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[11] 21 C.F.R. § 814 *et seq.* (devices); 21 C.F.R. § 600-680 (biologics); 21 C.F.R. § 314 *et seq.* (drugs).
[12] 21 U.S.C.A. § 814.20; 21 C.F.R. § 314.50; 21 C.F.R. § 601.2.
[13] 21 U.S.C.A. § 360e; 21 C.F.R. § 814.40-814.47.
[14] Accessories of devices intended to be used with Class II devices are regulated as Class II devices and require 510(k) clearance. To bundle a Class II device with its instruments as a KIT also requires 510(k) clearance. See FDA's "Medical Device Accessories: Defining Accessories and Classification Pathway for New Accessory Types Draft Guidance for Industry and Food and Drug Administration Staff" issued January 30, 2015 (http://www.regulations.gov) (ucm429672.pdf)

5. Premarket Approval (PMA) Letter and Restrictions

49. The FDA's PMA letter will include the restrictions for commercial marketing of the PMA-approved device. The sponsor's failure to adhere to the pre-market and post-market requirements for selling a product under an approved PMA may result in FDA's withdrawal of the PMA approval. The PMA approval also requires FDA to publish a summary of safety and effectiveness information (usually drafted by the Sponsor) it considered and on which the FDA's approval is based.

6. PMA Supplements for Changes

50. For an original PMA approval, the PMA supplement pursuant to 21 C.F.R. § 814.39 will be used to make significant changes to the original PMA product, label or manufacturing. One approved original PMA (or NDA) can have years of subsequent changes made by FDA's approval of supplements. The PMA supplements will essentially show the evolution of the original product(s) over time. The same serial supplement process does not apply to the 510(k). Significant changes to a 510(k) product or changes to address issues with safety and effectiveness of the device require FDA's clearance of a new 510(k).

51. The FDA approves the Sponsors proposed draft label to ensure it reflects the accuracy of the information provided by the Sponsor and considered by the FDA to support product approval. The Sponsor of the PMA approved product (as well as the NDA approved product) retains the ability at all times to comply with the Act and protect the public. The Sponsor can immediately update its own label to improve and strengthen the warnings and instructions for use or to delete false and misleading information from the FDA's approved label. This ability to update and circulate the new label before obtaining FDA's approval of the changes is done using a Supplement process called a "Changes Being Effected" Supplement. (Drug- 21 C.F.R. § 314.70; Device- 21 C.F.R. § 814.39)

52. There is no restriction, other than accuracy and truthfulness, for a Sponsor to directly communicate risk information, warnings, changes in the instructions for use directly to health care providers by communications such as Dear Health Care Provider letters, training, KOL, and through its own sales force. The goal is for the Sponsor should be to ensure product compliance and that its product remains safe, effective throughout the anticipated lifetime of the product, adequately labeled and that the public remains protected.

7. When 510(k) Changes Require A New 510(k) Clearance

53. The 510(k) letter also describes the restrictions for sale of the cleared device, including the Indications for Use, as well as other actions required by the sponsor including establishment of QSR and adequate labels. The 510(k) process has no formal mechanism for FDA withdrawal or removal once a product is 510(k) cleared. The manufacturer essentially takes over all actions for oversight and marketing of its 510(k) cleared product. The PMA has approved product labeling which under certain circumstances should be updated by the sponsor. The 510(k) has been cleared by FDA for an indication for use and specific marketing claims. As stated in the 510(k) clearance letter, it is the sponsor that is directly

responsible for ensuring its label remains adequate. The 510(k) sponsor for the majority of reasons, can immediately update and improve its label and marketing without receiving additional FDA input.

54. Significant changes to a 510(k), including ownership, changes which alter the intended use, new efficacy claims, change in the patient population, changes which raise new issues of safety and effectiveness and/or changes to a device made to address safety issues with a device are examples of when a Sponsor of a 510(k) cleared device is required to submit and obtain clearance of a new 510(k). When a Sponsor is in doubt if a new 510(k) is required, the FDA will provide guidance as to whether or not a new 510(k) is necessary. FDA also has returned submitted 510(k)s once it determined that a 510(k) submission was not necessary from a Sponsor.

8. Sponsors of PMA and 510(k)s Share Common Duties Under Quality Systems Regulations (21 C.F.R. § 820)

55. Both the PMA approval sponsor and the 510(k) clearance sponsor have shared responsibilities pursuant to the Quality System Regulations (QSR) for process controls, employee training, management responsibility, record keeping, post-market surveillance, maintaining complaint files, statistical trending and submission of Medical Device Reports (MDRs) to report adverse events and malfunctions to the FDA (21 C.F.R. § 803). Both sponsors share a common duty to update physicians and provide adequate and truthful warnings and instructions for use and ultimately ensure it continues to sell as safe, effective and adequately labeled device to the public.

9. 510(k) Clearance is Not Equivalent to PMA Approval and to Indicate Otherwise is "Misbranding"

56. FDA's 510(k) clearance letter plainly states that "clearance" of a device through a 510(k) is not the same as "*approval*" of a device by (PMA). FDA states for a 510(k) letter that: "[s]ubmission of a premarket notification . . . *does not in any way denote official approval of the device. Any representation that creates an impression of official* ***approval*** *of a device because of complying with the premarket notification regulations is misleading and constitutes misbranding.*" 21 C.F.R. § 807.97.

57. Accordingly, 510(k) "clearance" and PMA "approval" are two distinct and separate processes and outcomes. For a manufacturer to represent a 510(k) cleared product is approved by FDA as safe and effective is by regulation "misleading" and constitutes "misbranding" of the device.

B. FDA'S 510(K) PROCESS ADMITTEDLY HAS WEAKNESSES INCLUDING FDA'S REQUIRED RELIANCE ON THE 'TRUTHFULNESS AND ACCURACY' OF THE INFORMATION IN A SPONSOR'S PRE-MARKETING APPLICATION

58. Indeed, the 510(k) "clearance" process, as compared to an "approval" process, has undergone a great deal of scrutiny over the prior years, see discussion above by the GAO for SMDA. When the Medical Device Amendment was passed in 1976, it had been the expectation of Congress that the majority of medical devices would undergo the more rigorous PMA approval process or adhere to FDA-issued performance standards for that device before entering the market. Besides strengthening the adverse event reporting (AER, or MDR) requirements with SMDA, Congress also chose to address the pre-market role of industry to ensure adherence to adequate design controls including pre-production design validation and methods of risk management implemented later as the Quality System Regulations (QSR) (21 C.F.R. § 820). The emphasis of the Act and implementing regulations was shifted by Congress from the FDA's pre-market review to the role of industry for ensuring it sold safe and effective medical devices.

59. A variety of different independent analyses have continued to sound criticism of the 510(k) process and a call for substantive changes.[15] The resulting crescendo culminated recently in a FDA-requested analysis of the 510(k) process by the Institute of Medicine (IOM), a branch of the widely-respected National Academy of Sciences routinely contracted by FDA to provide it with outside expert recommendations. The IOM concluded that, "*the 510(k) process is flawed based on its legislative foundation*" and "*lacks the legal basis to be a reliable premarket screen of the safety and effectiveness…and cannot be transformed into one.*"[16] These recommendations are not unique, and have been echoed by the U.S. Government Accountability Office (GAO), physicians, and consumer groups.[17] The 510(k) process has also helped lock manufacturing and materials in the United States for medical devices into pre-1976 materials. Reliance on pre-1976 materials helps a Sponsor like Ethicon avoid having to do testing to support the safety and effectiveness of new biomaterials when proposed to be permanently implanted in patients. As an example, polypropylene (PE) synthetic surgical mesh is based on 'pre-Amendments' surgical mesh, a screen-like material, used to repair gapping abdominal wounds temporarily during Korea and the Viet Nam War which was 'grandfathered' as safe and effective for use as implanted surgical mesh.

60. For a period of time and prior to advancements in toxicology, immunology, laboratory methods and microbiology, physicians considered polypropylene mesh essentially "inert"

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[15] GAO testimony before the Subcommittee on Health Committee on Energy and Commerce, House of Representatives Medical Devices: Shortcomings in FDA's Premarket Review, Postmarket Surveillance, and Inspections of Device Manufacturing Establishments. Statement of Marcia Crosse, Director, Health Care June 18, 2009.

[16] Institute of Medicine (IOM), *Medical Devices and the Public Health: The FDA 510(k) Clearance Process at 35 years*, Washington, DC: National Academies Press, 2011, available at: http://www.nap.edu/catalog.php?record_id=13150. (last visited July 14, 2015).

[17] *See* U.S. Government Accountability Office, *Medical Devices: FDA Should Tae Steps to Ensure that High-Risk Device Types are Approved through the Most Stringent Premarket Review Process*, January 2009, available at: http://www.gao.gov/assets/290/284882.pdf (last visited July 15, 2015); *see also* DM Zuckerman et al., *Medical Device Recalls and the FDA Approval Process*, 171(11) Archives of Internal Medicine 1006-1011 (2011); JZ Hines et al., *Left to Their Own Devices: Breakdowns in United States Medical Premarket Review*, 7(7) Public Library of Science Medicine e1000280 (2010); Public Citizen, *Substantially Unsafe: Medical Devices Pose Great Threat to Patients; Safeguards must be Strengthened not Weakened, February 2012*, available at: http://www.citizen.org/documents/substantially-unsafe-medical-device-report.pdf (last visited July 15, 2015).

and well tolerated by the body. Science and follow-up has shown that the assumption that polypropylene was an inert material when implanted in the body was not accurate.

C. ETHICON HAS A 'NON-DELEGABLE' DUTY TO DEVELOP, DESIGN, TEST AND SELL A SAFE AND EFFECTIVE AND ADEQUATELY LABELED TVT-SECUR DEVICE TO PHYSICIANS INTENDED FOR PERMANENT IMPLANTATION IN PATIENTS

61. The FDA's 510(k) process by which the TVT-SECUR was cleared for sale in the United States by Ethicon on November 2005 admittedly has limitations; however, it was never intended that FDA's reviewer in completion of a 90-day review of a written 510(k) submission designed and authored by Ethicon could independently determine the accuracy and completeness of the information given to FDA by Ethicon. The FDA's reviewers, primarily without clinical experience or training, do not have a role to handle, test or use Ethicon's proposed new device(s) nor does anyone at the FDA have a role to conduct independent laboratory testing or clinical trials in patients as part of its 510(k) clearance process. It is an Ethicon employee required by FDA to sign a "Truthful and Accuracy Statement" in the 510(k) certifying Ethicon has provided FDA with all material information about the proposed product in the 510(k). Without the presence of an Ethicon signed Truthful and Accuracy Statement, and Ethicon 510(k) application cannot be even filed by FDA for future review.

62. The FDA's reviewer in ODE's surgical devices branch, assigned the task to complete a 510(k) submission review within 90 days, must rely on Ethicon's Truthful and Accuracy certification, as well as Ethicon's knowledge and experience as the expert and designer of the TVT-SECUR and other similar products to be willing and able to provide FDA with adequate and complete disclosure about the device it intends to market. FDA must assume that Ethicon intends to sell a safe and effective product for permanent sub-urethral implantation in patients in the United States. The FDA reviewer is also aware that it is a Prohibited Act (21 U.S.C. § 331(a)(b)) for Ethicon to sell a medical device in the United States that is not safe, effective and adequately labeled. As part of the 510(k) process, Ethicon's commitment to adherence to Quality Systems must only be assumed by FDA's ODE reviewer, since that information is not required to be provided by Ethicon in the 510(k), nor is it required to be reviewed or verified at time of FDA's review of the 510(k). Therefore, despite obtaining 510(k) clearance from FDA, it remains Ethicon's non-delegable duty (not the FDA's) to ensure the device it intends to manufacture and commercially sell in the United States will actually performs as it described the device to FDA and was cleared by its 510(k) when implanted in a patient. It is Ethicon's role (not the FDA's) to ensure that there are no new unaddressed issues of safety and effectiveness for the commercial product which would render its product adulterated and misbranded. If (or when) Ethicon knows that the TVT-SECUR System does not perform as described to FDA and cleared by the 510(k) (K052401) after November 28, 2005 as a sub-urethral sling for SUI, then Ethicon (not the FDA) is selling a misbranded and adulterated product(s). Ethicon's commercial product must legally perform as described and cleared by its own 510(k).

63. The 510(k) process review hinges on the meaning of a product's 'intended use'. For example, Ethicon claimed that TVT-SECUR was a Prolene polypropylene mesh tape with the ends of the device sandwiched between pieces of fleece made of polyglactin 910/poldioxanone coated with polydioxanone film. This material added to Ethicon's PROLENE surgical mesh had been adapted from Ethicon's already cleared dura replacement material (fleece) intended for covering defects in the covering of the brain and was sold as "Ethisorb". The Ethisorb coated ends were to facilitate passage (stiffen the Prolene mesh ends) and placement (improved tactile feel for a surgeon) of the mesh implant for sub-urethral sling for SUI. The tape was to be implanted using curved, stainless steel introducers fixed to the implant via a wire through the coated ends and inserters. TVT-SECUR differed from Ethicon's cited predicates (TVT and TVT-O) in that it was designed to accommodate the two different surgical techniques for treatment of SUI in one system: the shorter "hammock approach" sling of TVT-Obturator and the longer "U" approach and sling of TVT. FDA was told that the TVT-SECUR Universal System is a less invasive "exit less" device which would allow the surgeon to perform a suburethral sling method by either approach, placing a Prolene mesh sling, long or short, under the mid urethra without either the delivery device or the implant exiting the skin. The new intended use for TVT-SECUR and claims of less invasive procedure with an exit less device, first required clearance of a new 510(k) by FDA for marketing.

64. Ethicon's 510(k) initially provided as the legally marketed predicates TVT (K974098) and TVT-O (K033568) both already cleared for the same intended use (SUI) and the history of their marketing as support of safety and effectiveness for this intended use for TVT-SECUR so it could be cleared by a 510(k). Ethicon called TVT-SECUR, an 8cm mini Tape placed by a single incision, only a modification of the TVT products for treatment of SUI. Ethicon also cited (bridged) the clearance and implant commercial history of its Codman Ethisorb Dura Patch (synthetic absorbable implant) (K991413). Ethisorb had been cleared on March 8, 2000 by FDA to be sold as a dura mater (brain) replacement material for bridging defects (holes) of the dura mater. Ethicon's bridging claimed that Ethisorb (a fleece material) could be implanted permanently in a human, even in the pelvis. Ethisorb also contained Vicryl and PDS absorbable material (910/polydioxanone) approved for Ethicon as two absorbable sutures. However, Ethicon as the knowledgeable expert was required to know and inform the FDA's review of differences in Ethisorb, as a sutured and passive dural replacement when new proposed function was to help stabilize a moving Ethicon TVT sub-urethral sling in a patient's pelvis until the sling has sufficient tissue ingrowth to permanently stabilize the mesh sling to treat symptoms of SUI.
65. After a clinical review by Medical Officer Dr. Herrera, also a urologists, the FDA in a letter of October 2005 requested that Ethicon provide clinical data with 12 months follow up to support the performance of TVT-SECUR in order to obtain 510(k) clearance. However, Ethicon's response form Martin Weisberg, M.D. was to update the information for its sheep study and provide a new predicate a Gyne Ideas Mini Tape, a 14cm mini tape cleared in 2003 by FDA without requiring long-term clinical data.

66. The 510(k) clearance did not address the use of Ethisorb for a stabilization role. However, Ethicon's use of Ethisorb in the TVT-S design was to create a less invasive 'exit less placement' device. Despite the statement in the 510(k), the new use of Ethisorb as marketed

by Ethicon would raise new issues of safety and effectiveness for the performance and marketing of TVT-SECUR for its new clinical use of Ethisorb as well as capability for a surgeon to place the TVT and TVT-O without an exit from the skin. This new proposed change to the use of Ethisorb as well as Ethicon's use of a new term such as "Universal System" (capable of placement with the same mesh sling as either the shorter sub-urethral "H" hammock [TVT-O approach] or "U" shaped longer sling of TVT). These changes and foreseeable new risks required Ethicon before it sold TVT-SECUR in the United States to ensure there was sufficient development and testing to be able to provide surgeons with an adequate label and thorough instructions for use, warnings and precautions as well as a method for adequate training of physicians and its own salesforce. FDA's 21 C.F.R. § 801.4 (meaning of "intended use").

67. The words intended use or words of similar import in §§ 801.5, 801.119, and 801.122 refer to the objective intent of the persons legally responsible for the labeling of devices. The intent is determined by such persons' expressions or may be shown by the circumstances surrounding the distribution of the product. This objective intent may, for example, be shown by labeling claims, advertising matter, or oral or written statements by such persons or their representatives. It may be shown by the circumstances that the product is, with the knowledge of such persons or their representatives, offered and used for a purpose for which it is neither labeled nor advertised. The intended uses of a product may change after it has been introduced into interstate commerce by its manufacturer. If, for example, a packer, distributor, or seller intends an article for different uses than those intended by the person from whom he received the devices, such packer, distributor, or seller is required to supply adequate labeling in accordance with the new intended uses. But if a manufacturer knows, or has knowledge of facts that would give him notice that a device introduced into interstate commerce by him is to be used for conditions, purposes, or uses other than the ones for which he offers it, he is required to provide adequate labeling for such a device which accords with such other uses to which the article is to be put

III. OVERVIEW OF MY ROLE AS A FDA REGULATORY EXPERT

68. I view my primary role as a FDA regulatory expert in this litigation as providing a regulatory discussion of the FDA's and medical device manufacturer's framework as it relates to the Federal Food Drug and Cosmetic Act (the Act), implementing regulations, FDA, industry and the public. This discussion is supported by my own training, experience and history of activities both while at FDA and after leaving FDA. Congress by passage of the Medical Device Amendments of 1976 to the Act assigned FDA a specific role to be the public's gatekeeper controlling the entry of medical devices into the United States. The FDA was charged to develop necessary regulations and frameworks for industry to use to bring new medical devices to market for the use of the public and to facilitate that the devices were adequately designed, manufactured, monitored and labeled. Congress placed limitations on the reach of FDA's authority, and as a government agency the FDA has practical restrictions placed on its funding and resource allotment. Congress placed the primary responsibility for ensuring compliance with the Act not on the FDA but on each medical device manufacturer, the entity engaged and profiting from the successful design, manufacture, distribution monitoring and sale of its medical devices. All United States medical device manufacturers are required to establish and adhere to internal methods for

ensuring compliance with the Act and implementing regulations. Each medical device manufacturer is required to create and adhere to its own standard operating procedures (SOP) for product design, manufacturing, oversight, reporting, record keeping, failure investigation with the ultimate goal to ensure it sells safe and effective medical devices, will voluntarily update labels and marketing and take steps to protect the public from harm. It is a 'Prohibited Act' for any medical device manufacturer, including Ethicon and Johnson & Johnson, to sell medical devices in the United States that are not safe, effective, adequately designed, manufactured and labeled and in full compliance with the Act. (21 U.S.C. § 331(a)(b)).

69. The first area of my anticipated testimony will include, but not be limited to, general discussion of FDA's overall mission to protect the public; its history of reliance on a risk-based device classification paradigm as well as to describe pertinent regulatory terms for TVT-SECUR such as: '510(k)', 'IDE', 'PMA', 'clinical trials', preclinical', 'IRB', 'adequate informed consent', 'foreign data', 'label', 'marketing', 'new claims', 'intended use', 'substantial equivalence (SE)', 'not substantially equivalent (NSE)', 'safety and effectiveness', 'raising new issues of safety and effectiveness', 'review clock', 'Class III', 'investigational', 'note to file', 'clearance', 'approval', 'Quality Systems', 'Good Manufacturing Practices', 'Medical Device Reporting'(MDR), 'FDA Advisory Committees (AdCom)', 'predicate', 'post-market surveillance', '522 Order', 'reclassification', 'safety signal', 'warning', 'precaution', 'instructions for use', failure effects mode analysis (FEMA), 'risk management', 'failure investigation', 'corrective and preventive action (CAPA)', 'design', 'complaint', Medical Device User Fee Amendment (MDUFA), 'regulatory hold', 'health risk', 'supplement', 'Dear Health Care Provider Letter', and 'off-label'. I will describe the role of various Offices in FDA's Center for Devices and Radiological Health (CDRH) as well as members of Office of Device Evaluation (ODE), 510(k) reviewers, the standard used by FDA's reviewers to consider clearance and the procedure and completion of a 510(k) Determination Flow sheet as part of the official 510(k) record to support FDA's decision making. Other general issues which may be covered and as related to TVM SUI and TVT-SECUR include FDA's general use of compliance and enforcement actions, and enforcement discretion including Warning Letters, FDA facility inspections, observations listed in FDA Form 483, and the differences between mandatory versus voluntary recalls; FDA's reliance on issuance of public notifications as an expedient regulatory action (tool); medical device safety and efficacy as applicable to industry standards and quality systems; pre- and post-market regulatory requirements in terms of adequate study, design, comparison to predicates, introduction and disclosure of new issues of safety and effectiveness, the limitations of 510(k) clearance and duties for commercial marketing applicable to all medical device manufacturers; FDA's ability to reach out directly to health care providers and patients using vehicles such as Public Health Notifications and Safety Alerts to warn about the potential risks of devices including lack of long-term safety and efficacy data; FDA's ability to use public FDA Advisory Committee meetings for publicity and to solicit outside expert opinions about issues, for example the use of TVM for SUI, pelvic floor repair (PFR) and pelvic organ prolapse (POP) products; FDA's use of reclassification of devices for TVM POP based on new risk concerns or new benefits and controls; FDA's ability to reclassify previously exempted products to require

clearance of a 510(k); FDA's authority to issue a 522 Order to require a Sponsor (or an entire industry) to conduct studies to obtain post-market safety and efficacy information.

70. As it is required, there will be more general discussions regarding the regulatory history of Ethicon's synthetic surgical suture Prolene and Prolene surgical mesh,[18] clearance of synthetic surgical mesh as pre-Amendments (pre-1976) product. Ethicon's use of Prolene polypropylene mesh for products intended as transvaginal mesh (TVM) of a tension free vaginal mesh tape (TVT). Ethicon's clearance of a minimally invasive surgical (MIS) procedure kit with mesh tape and insertion instruments introducer and two stainless steel needles, and instructions for physicians as a sling SUI procedure system (K974098). TVT implanted a 'U' shaped mesh pubourethral sling,(citing as predicate "ProteGen Sling Collagen Impregnated Material"- voluntarily withdrawn from the market by the sponsor due to safety issues -1999). There may be general discussion of the principle of TVT mesh for tissue ingrowth through the mesh pores following a period of implantation in the pelvis to hold the tape sling "tension free" in a woman's pelvis to help treat her symptoms of SUI. Ethicon later modified the surgical insertion approach for a surgeon to an 'obturator' approach to implant a shorter 'H" shaped (hammock) sub-urethral sling. This new approach and sling would be marketed as TVT-Obturator (O) cleared on December 8, 2003 (K033568). Both of these Ethicon TVM TVT tape Prolene SUI slings exited through the woman's skin. Ethicon's next TVT product was the TVT-SECUR. It continued the same principles of Ethicon's other MIS tape mesh TVT products however, there was no exit (i.e. exit less) from the woman's skin by the insertion approach. Also Ethicon called the TVT-SECUR, its Universal System with the tape able to be used by a surgeon to implant minimally invasively as either a TVT U or TVT-O H sling. For TVT-SECUR Ethicon also had incorporated Ethisorb (absorbable fleece material) at each end of the Prolene mesh sling to help the surgeon move it and then to hold it in place until there was sufficient tissue ingrowth. The Ethisorb material at some time would be absorbed (Vicryl and PDS Suture) and the system still able to be called 'tension free'.

71. As a FDA medical regulatory expert, and as requested I will provide regulatory overviews of the United States history and evolution of Ethicon's (SUI) products including its reliance on FDA's Guidance, including the FDA's Surgical Mesh Guidance, pelvic industry predicates, global industry standards, and marketing claims to physicians and requirement for Ethicon to balance benefit claims with risk information; absorbable Ethisorb as dura patch implant and Ethicon's adaptation to create a partially absorbable component for the Prolene mesh tape; FDA's required use of the "Least Burdensome method" for industry and Ethicon's ability as the knowledgeable expert to reference (bridge) information already contained in its prior cleared and approved marketing applications in lieu of conducting duplicate testing; FDA's requirements for Ethicon to obtain clearance of 510(k)s before start of marketing and then to continue to market the product that was cleared by the FDA in the 510(k) in the United States; Ethicon's creation and implementation of internal standard operating procedures (SOP) to develop, design, test, manufacture and control TVT-SECUR medical devices for SUI based on Ethicon's use of FDA's minimal Quality Systems Regulations (QSR) (21 C.F.R. 820); the evidence that supports my expert opinions about Ethicon's

[18] Ethicon's Prolene™- first used in commerce by Ethicon and Trade Marked for Prolene Sutures in 1968; first used and Trade Marked for Prolene Surgical Mesh in 1975.

adherence (or lack of adherence) to accepted methods for industry design and risk management; examples of Ethicon's evidence of risk management procedures for TVT-SECUR including postmarket surveillance, monitoring, complaint handling, failure investigation, medical device reports (MDRs), statistical trending, identification and completion of adequate corrective and preventive actions (CAPA); Ethicon's continuing ability and duty to update its own product labels, marketing and salesforce for surgeons and women to provide adequate risk information and warnings; Ethicon's duty to provide prescribers with adequate prescription labels and surgical training as well as its duty to train and update its own salesforce; Ethicon's history of interactions with FDA and physicians regarding risks and benefits of TVT-SECUR; Ethicon's continuing ability to ensure its own compliance with the Act and voluntarily update its own labeling, salesforce, marketing; Ethicon's ability to discontinue sales or voluntarily withdraw and/or recall TVT-SECUR from the United States market. The global industry standards and my professional experience and training provide a substantial foundation for the bases of my opinions.

72. In terms of the history of interactions between FDA and Ethicon for TVM, SUI as well as POP, as required I will provide a discussion of FDA's use of notification processes and/or public statements concerning spreading concern about potential risks of TVM for SUI and POP; the history of FDA's Advisory Committee Panel and conclusions for Trans-Vaginal Tape (TVT) for SUI (and TVM for POP); FDA's issuance of 522 orders to Ethicon as well as the TVM industry to specifically obtain post-market safety and efficacy information for TVT-SECUR implanted in women; Ethicon's decision to opt to voluntarily stop selling (de-commercialize) the TVT-SECUR in lieu of fulfilling FDA's request it obtain post-market safety and efficacy information for its SUI products implanted in women.

73. Additionally, I may provide discussion regarding relevant regulatory matters relating to TVT-S as discussed in my expert report(s) and/or disclosures in this case and previous cases and the following opinions. I specifically adopt my testimony in the case *Sandra Garcia v. Rodolfo Walss, M.D., et al.*, Cause No. 2013-DCL-3511-D, District Court of Cameron County, Texas [103rd District]. I may also respond to testimony and opinions of Defendant's experts within my subject matter expertise. For a specific plaintiff, I will attempt to limit my discussions and opinions to the timeframe appropriate to the patient's implantation and when relevant to explant. I will testify that all my expert opinions, including the eight (8) below, are all made to a reasonable degree of regulatory, professional and medical certainty.

IV. OPINIONS

1. OPINION # 1:

ETHICON's 510(K) FAILED TO ADEQUATEDLY DESCRIBE A FULL AND ACCURATE DISCLOSURE OF THE MANY SIGNIFICANT DIFFERENCES BETWEEN TVT-SECUR (A NEW SIS MINI TAPE) AND THE TVT AND TVT-O SYSTEMS PREDICATES ORIGINALLY CITED BY ETHICON. ETHICON FAILED TO DESCRIBE RISKS TO FDA ASSOCIATED WITH THE DEVICE PRIOR TO CLEARANCE. DESPITE THE FORESEEABLE AND UNANSWERED RISKS REMAINING FOR

IMPLANTING WOMEN WITH A NEW MINI SLING, ETHICON WAS ABLE TO REFERENCE GYNE IDEAS' MINI TAPE DEVICE AS A PREDICATE AND AVOID OBTAINING CLINICAL DATA PRIOR TO 510(K) CLEARANCE.

Applicable Regulations: 21 C.F.R. § 807; 21 U.S.C. § 352(t); 21 U.S.C. § 331(a)(b); 21 C.F.R. § 820; 21 C.F.R. § 801.4; 21 C.F.R. § 812[19]

2. **OPINION #2:**

ETHICON KNEW THERE WERE NEW RISKS FOR SIS MINI SLING WHEN COMPARED TO TVT AND TVT-O SYSTEMS BASED ON CHANGES MADE TO HELP REDUCE COSTS. HOWEVER, ETHICON CHOSE NOT TO STUDY THE IMPACT OF THOSE CHANGES FOR PATIENT SAFETY. ETHICON DID NOT UPDATE ITS TVT-SECUR IFU TO ADEQUATELY WARN OF INCREASED RISKS FOR PREMATURE FAILURE, CHRONIC PAIN, DYSPAREUNIA, MESH EXTRUSION AND EROSION, CHRONICITY AND WORSENING OF SYMPTOMS, DIFFICULTIES WITH MESH REMOVAL, DIFFICULTIES WITH INSERTER FUNCTION AND PATIENT NEED FOR ADDITIONAL SURGERY.

Applicable Regulations: 21 C.F.R. § 807; 21 U.S.C. § 331(a)(b); 21 C.F.R. § 801.109; 21 C.F.R. § 820

3. **OPINION #3:**

ETHICON, DESPITE HAVING MADE SPECIFIC ASSURANCES TO ITS OWN MEDICAL INVESTIGATORS THAT CERTAIN ADDITIONAL SAFETY STUDIES WOULD BE PERFORMED DID NOT LIVE UP TO THAT AGREEMENT.

Applicable Regulations: 21 C.F.R. § 812; 21 U.S.C. § 352(a)(f)(1)(2); 21 U.S.C. § 331(a)(b); 21 C.F.R. § 801.109; 21 C.F.R. § 820

4. **OPINION # 4:**

ETHICON'S MARKETING FOR TVT-SECUR TARGETED SURGEONS WITHOUT REGARD AS TO PELVIC SURGERY EXPERIENCE, MINIMIZING DIFFICULTIES FOR PLACEMENT OF THE MINI SLING, INACCURATELY CALLING IT 'LESS INVASIVE' WHILE KNOWING THE PROCEDURE HAD A SIGNIFICANT SURGEON LEARNING CURVE, THE 'U' APPROACH WAS HARDER TO PERFORM THAN THE 'HAMMOCK', DIFFICULTIES WERE

[19] As I previously explained, there are also a number of industry standards that support each of my opinions. For brevity, I have listed these in my reliance list and inserted a discussion of these guidelines, where applicable.

REPORTED WITHDRAWING THE INSERTER WITHOUT DISPLACING THE MINI SLING. ETHICON SELECTIVELY PROVIDED SOME SURGEONS WITH UPDATED INSTRUCTIONS AND SURGICAL TIPS WHILE ETHICON FAILED TO ADEQUATELY UPDATE ITS OWN LABEL, IFU AND MARKETING AND SALES FORCE TO WARN 'ALL' SURGEONS EQUALLY OF TVT-SECUR INCREASED RISKS COMPARED TO OTHER TREATMENT OPTIONS FOR SUI. FINALLY, ETHICON FAILED TO WARN SURGEONS ABOUT PATIENT RISKS FOR MESH EXTRUSION, EROSION, CHRONIC PAIN, WORSENING OF SYMTPOMS, DYSPAREUNIA AND NEED FOR ADDITIONAL SURGERY.

Applicable Regulations: 21 U.S.C. § 352(a)(f)(1)(2); 21 U.S.C. § 321(n); 21 U.S.C. § 331(a)(b); 21 C.F.R. § 801.109; 21 C.F.R. § 820

5. **OPINION #5:**

DESPITE ETHICON'S KNOWLEDGE OF POST-MARKET DIFFICULTIES FOR THE TVT-SECUR SYSTEM, INCLUDING HIGH FAILURE RATE, BLADDER PERFORATIONS, COMPLAINTS FROM ITS OWN TRAINED KEY OPINION LEADERS (KOL), AND THAT EUROPEAN SURGEONS HAD STOPPED PERFORMING TVT-SECUR IN 2007 BASED ON UNACCEPTABLE RISKS, ETHICON CONTINUED TO MARKET TVT-SECUR IN THE UNITED STATES WITHOUT NOTIFYING SURGEONS OR PATIENTS ABOUT THE INCREASED RISKS. ETHICON DID NOT VOLUNTARILY CONDUCT POST-MARKET SURVEILLANCE STUDIES IN ORDER TO UDPATE ITS AMERICAN LABEL, PHYSICIANS AND WOMEN WITH ACCURATE RISK INFORMATION.

Applicable Regulations: 21 C.F.R. § 803; 21 U.S.C. § 352(a)(f)(1)(2)(t); 21 U.S.C. § 321(n); 21 U.S.C. § 331(a)(b); 21 C.F.R. § 801.109; 21 C.F.R. § 820.198; 21 C.F.R. § 820.250

6. **OPINION #6:**

BASED ON ETHICON'S MISREPRESENATIONS TO ITS SALES FORCE AND PHYSICIANS AS WELL AS FDA, INCLUDING ITS FAILURE TO CONSIDER AND DISCLOSE THAT THE MOST EXPERIENCED SURGEONS WITH TVT-SECUR EXPERIENCED DIFFICULTIES AND PREMATURE FAILURES WITH THE DEVICE, IMPLANTING SURGEONS WOULD NOT HAVE BEEN ABLE TO PROVIDE A PATIENT WITH AN ADEQUATE INFORMED CONSENT BASED ON KNOWLEDGE OF THE RISKS OF THE TVT-SECUR PRODUCT AS A SIS MINI SLING FOR SUI.

Applicable Regulations: 21 U.S.C. § 352(a)(f)(1)(2); 21 U.S.C. § 321(n); 21 U.S.C. § 331(a)(b); 21 C.F.R. § 801.109; 21 C.F.R. § 820.198; 21 C.F.R. § 820.250; 21 § C.F.R. 50

7. **OPINION #7:**

SURGEONS RELIED ON THE KNOWLEDGE, SKILL AND EXPERIENCE OF ETHICON AS A MAJOR UNITED STATES MEDICAL DEVICE MANUFACTURER TO, ADEQUATELY INFORM THEM OF THE RISKS FOR TVT-SECUR AND PROVIDE PHYSICIANS WITH SAFE AND EFFECTIVE PRODUCTS TO PERMANENTLY IMPLANT IN WOMEN.

Applicable Regulations: 21 C.F.R. § 820.198; 21 C.F.R. § 820.250; 21 C.F.R. § 803; 21 C.F.R. § 820.100; U.S.C. § 352(a)(f)(1)(2); 21 U.S.C. § 321(n); 21 U.S.C. § 331(a)(b); 21 C.F.R. § 801.109

8. **OPINION #8:**

FDA ISSUED A 522 ORDER TO COMPEL ETHICON TO OBTAIN POST-MARKET PERFORMANCE INFORMATION FOR TVT-SECUR MINI SLING TO UDPATE THE LABEL. ETHICON'S MANAGEMENT HOWEVER CHOSE TO DECOMMERCIALIZE (STOP SALES) OF TVT-SECUR. ITS ACTION HALTED THE 522 PROCESS AND ETHICON DID NOT COMMIT TO OBTAINING ANY OTHER POST-MARKET PERFORMANCE INFORMATION FOR WOMEN ALREADY IMPLANTED. AFTER STOPPING SALES OF TVT-SECUR ETHICON CONTINUED NOT TO ADEQUATELY NOTIFY PHYSICIANS OR WOMEN ABOUT THE RISKS ASSOCIATED WITH TVT-SECUR.

Applicable Regulations: 21 C.F.R. § 820.198; 21 C.F.R. § 820.250; 21 C.F.R. § 803; 21 C.F.R. § 820.100; U.S.C. § 352(a)(f)(1)(2); 21 U.S.C. § 321(n); 21 U.S.C. § 331(a)(b); 21 C.F.R. § 801.109; 21 C.F.R. § 1.21; 21 C.F.R. § 822.3(j); 21 U.S.C. § 360l

V. SIGNATURE

74. I reserve the right to amend or supplement this report and eight opinions in the event that additional pertinent information becomes available or additional issues are raised in reports of other experts. All opinions are made to a reasonable degree of professional and regulatory certainty.

Suzanne Parisian, M.D.

1-30-2016
Date

75. Each of these eight opinions is discussed individually below along with the bases supporting the opinion.

VI. BASES FOR OPINIONS

A. OPINIONS 1, 2 & 3: ETHICON'S PREMARKET ROLE WITH DEVELOPMENT OF TVT-SECUR AS A NEW SINGLE INCISION MINI SLING

OPINION # 1:

ETHICON's 510(K) FAILED TO ADEQUATEDLY DESCRIBE A FULL AND ACCURATE DISCLOSURE OF THE MANY SIGNIFICANT DIFFERENCES BETWEEN TVT-SECUR (A NEW SIS MINI TAPE) AND THE TVT AND TVT-O SYSTEM PREDICATES ORIGINALLY CITED BY ETHICON. ETHICON FAILED TO DESCRIBE RISKS ASSOCIATED WITH THE DEVICE PRIOR TO CLEARANCE. DESPITE THE FORESEEABLE AND UNANSWERED RISKS REMAINING FOR IMPLANTING WOMEN WITH A NEW MINI SLING, ETHICON WAS ABLE TO REFERENCE GYNE IDEAS' MINI TAPE DEVICE AS A PREDICATE AND AVOID OBTAINING CLINICAL DATA PRIOR TO 510(K) CLEARANCE.

OPINION #2:

ETHICON KNEW THERE WERE NEW RISKS FOR SIS MINI SLING WHEN COMPARED TO TVT AND TVT-O SYSTEMS BASED ON CHANGES MADE TO HELP REDUCE COSTS. HOWEVER, ETHICON CHOSE NOT TO STUDY THE IMPACT OF THOSE CHANGES FOR PATIENT SAFETY. ETHICON DID NOT UPDATE ITS TVT-SECUR IFU TO ADEQUATELY WARN OF INCREASED RISKS FOR PREMATURE FAILURE, CHRONIC PAIN, DYSPAREUNIA, MESH EXTRUSION AND EROSION, CHRONICITY AND WORSENING OF SYMPTOMS, DIFFICULTIES WITH MESH REMOVAL, DIFFICULTIES WITH INSERTER FUNCTION AND PATIENT NEED FOR ADDITIONAL SURGERY.

OPINION #3:

ETHICON, DESPITE HAVING MADE SPECIFIC ASSURANCES TO ITS OWN MEDICAL INVESTIGATORS THAT CERTAIN ADDITIONAL SAFETY STUDIES WOULD BE PERFORMED DID NOT LIVE UP TO THAT AGREEMENT.

1. Overview of Ethicon's Clearance of Tension Free Vaginal Tape (TVT) Systems for SUI

76. The FDA regulatory history of Ethicon's TVT-SECUR actually begins with Prolene, polypropylene (PPE), a synthetic resin (plastic) material. Ethicon's Prolene was a synthetic surgical PPE suture originally regulated as a drug prior to the MDA of 1976. Considered as a new drug, Ethicon's Prolene as a nonabsorbable polypropylene suture obtained approval for marketing in the United States as a new drug by FDA's approval of a New Drug Application (NDA). With the pre-market regulation of medical devices after MDA of 1976, the approved Prolene suture NDA as a drug was transitioned to FDA regulation as an approved medical device. The Ethicon approved NDA (21 C.F.R. §314) for Prolene was changed to an approved Premarket Approval Application (PMA) (21 C.F.R. §814). Eventually, FDA down-classified sutures including the PMA approved Ethicon Prolene suture (Class III device) to class II, so that sutures were able to be cleared by FDA as 510(k)s.

77. Ethicon's Prolene surgical mesh[20] obtained clearance as a synthetic surgical mesh. Ethicon was able to bridge the NDA/PMA approval of Prolene polypropylene as an implant in the body for use in implanted surgical mesh. Surgical mesh had been sold intended for general surgical mesh for hernia repair beginning in the 1950s and prior to MDA of 1976 and regulation of medical devices by FDA. Therefore, surgical mesh is called a 'pre-

[20] Ethicon's Prolene™- first used in commerce by Ethicon and Trade Marked for Prolene Sutures in 1968; first used and Trade Marked for Prolene Surgical Mesh in 1975.

Amendments (pre-1976) product'. As a pre-amendments product, surgical mesh for general surgery and hernia repair and defect repair was grandfathered as safe and effective for that intended use. Based on risk it was classified by FDA as a Class II pre-Amendments device and all general synthetic surgical mesh for hernia repair were able to be cleared by 510(k).

2. Ethicon's Clearance of Its TVT System Based on Claims of Substantial Equivalence to ProteGen

78. Ethicon would submit a 510(k) (K974098) which proposed a new intended use of its already cleared Prolene polypropylene surgical mesh, a use in the pelvis. Ethicon was able to reference the prior history of permanent implantation of polypropylene Prolene surgical mesh in a patient to support safety for the new intended use. For a period of time, polypropylene as well as Prolene surgical mesh were incorrectly considered by physicians as biologically inert material when implanted in a patient. It was known that Prolene surgical mesh would trigger tissue ingrowth through the fabric's pores when implanted in the abdomen or inguinal areas and this ingrowth would help provide support for defects (gaps) in tissue. At the surgeon's option the surgical mesh could remain permanently implanted in patients. It was also known that if synthetic Prolene surgical mesh came directly in contact with the surface of the patient's bowel, there would be florid tissue ingrowth could involve the bowel and create serious complications including obstruction, fistula and necessitate additional surgery and difficulty with mesh removal.

79. Ethicon proposed a new use for narrow strips of Prolene (tape). The Prolene tape could be implanted transvaginally as a sling to help hold up the urethral to reduce symptoms of SUI. Ethicon called this a tension free vaginal tape (TVT). The passage of the needle for retropubic insertion of a tape sling by a surgeon could be either vaginally and up (down- up) or (top-down) to facilitate placement of a U shaped mid urethra sling. The sling was of polypropylene and could be placed minimally invasively by surgeons using multiple incisions with the sling ends exiting the patient's skin. The anticipated tissue ingrowth into the tape's mesh pores would help stabilize the sling in place to reduce mobility of the urethral and the angle to reduce symptoms of SUI. The TVT System also included specific insertion tools for a minimally invasive procedure kit to treat SUI. In contrast to the evolution of urological surgical procedure by surgeons to treat SUI, Ethicon was proposing to market a brand new surgical procedure kit for SUI with Ethicon providing instructions and training in its procedure for surgeons. Ethicon became essentially responsible for the introduction of a new surgical procedure for treating SUI. It also became responsible for training surgeons willing to purchase and try the kit other than trained urologists, essentially producing a new urogynecological procedure.

80. To clear the 510(k) for Ethicon, FDA's ODE reviewer requested no information on the Prolene surgical mesh sling but short-term clinical or animal data from Ethicon to support the feasibility that Ethicon's proposed TVT tape procedure could be learned and used by surgeons to implant a Prolene sling with Ethicon's accessories and instructions. Ethicon provided published data from the clinical use of the TVT kit performed outside the United States to support successful use by surgeons of its proposed kit.

81. Ethicon's 510(k) cited a predicate already FDA cleared synthetic fabric intended to create a pubourethral sling for treatment of SUI, a medical textile fabric sold as "ProteGen" (K963226). ProteGen had been cleared for Sponsor Boston Scientific Company (BSC) on November 15, 1996 as a surgical fabric. The fabric was a bovine impregnated collagen synthetic knitted fabric. ProteGen would be sold by BSC to be implanted as part of a new minimally invasive surgical procedure kit to treat SUI by BSC. Unlike TVT, the ProteGen sling was anchored in place by cleared Vesica bone anchors. BSC had been able to bridge marketing ProteGen fabric as a 'permanent implant fabric' based on PMA approved and 510(k) cleared surgical collagen impregnated vascular graft knitted mesh fabric sold commercially as Hemashield (manufactured by Meadox Medicals which was subsequently acquired by BSC). Hemashield had collagen impregnation to reduce the amount of blood required (i.e. lost) to implant a vascular graft. The use of ProteGen as a permanently implanted general surgical mesh, as with Prolene mesh, could be linked back to the pre-Amendments class II synthetic surgical meshes. However, citing a recently cleared mesh with an expanded indication, BSC's 510(k) clearance included new indications of pubourethral support, urethral and vaginal prolapse repair, reconstruction of the pelvic floor, bladder support and sacrocolposuspension. Because there was a predicate which had managed to obtain FDA's clearance of a 510(k) for those new indications for urogynecologic use, BSC could also obtain clearance of its ProteGen surgical mesh for those expanded indications in the pelvis.

82. ProteGen was cleared by 510(k) and used as a sling in a Procedure kit which included insertion instruments and bone anchors for treatment of SUI. Surgeons of all different medical backgrounds and training were taught a new minimally invasive insertion technique by BSC to treat women with symptoms of SUI. However, despite the commercial success of ProteGen and willingness of surgeons to learn to insert the product, it was quickly learned by physicians that the ProteGen failure rate was unacceptable. As Ethicon would have been aware, competitor BSC voluntarily withdrew ProteGen from the urogynecological market in January 1999. Despite BSC's marketing benefit claims, BSC's ProteGen when implanted in the female pelvis as an anchored bladder sling in the moving female pelvis, unlike its prior use as a Hemashield vascular graft perfused with blood, did create an acceptable sling to treat symptoms of SUI. Complaints with ProteGen included dyspareunia, erosions, extrusions, chronic pain, premature device failure, worsening of SUI symptoms and need for additional surgery. Ethicon, competing with BSC and ProteGen, beginning with TVT System was well aware of ProteGen's unacceptable performance, these reasons for its withdrawal and unacceptable performance as a sling for SUI. Ethicon should have been aware of the ProteGen history as it developed and tested its TVT-S System.

83. Ethicon's clearance of its TVT System on January 28, 1998 permitted it to market a minimally invasive surgical (MIS) procedure kit. It utilized a narrow strip of mechanically cut Prolene mesh tape and insertion instruments (an introducer and two stainless steel needles). Ethicon provided training and implant instructions for all physicians willing to learn how to perform a new sling SUI procedure (K974098). TVT implanted a 'U' shaped mesh sub-urethral sling by multiple incisions. As with Prolene in general, the principle of the Tension Free Vaginal tape (TVT) continued to utilize the patient's own natural immune response over time for tissue ingrowth through the tape's mesh pores as a foreign body

response. As with ProteGen, the reason for insertion of the mesh as a sling was to help hold and stabilize the bladder's urethra to help reduce symptoms of SUI. Unlike ProteGen, TVT used tissue ingrowth and not metal anchors. However, it usually takes about 12 weeks for the tension free procedure to develop enough tissue ingrowth to function to help reduce symptoms of SUI.

84. In Ethicon's Draft GYNECARE Value Proposition Report Project TVTx of November 9, 2004, there is Ethicon's discussion of seven known patient deaths associated with use of its TVT System:

> *As of May 31, 2004, seven deaths are associated with GYNECARE TVT. Six cases were for bowel perforation. Five were associated with undiagnosed bowel perforations at time of surgery. In the sixth case of bowel perforation, no additional information could be obtained. The seventh case was associated with a woman who had a bleeding disorder who died of uncontrolled postoperative bleeding in the retropubic space.*[21]

3. Ethicon's Clearance of TVT-O Based on Claims of Substantial Equivalence to TVT

85. Ethicon later modified the its TVT System surgical insertion approach for surgeons to a more lateral 'obturator' membrane approach, still requiring multiple incisions by a surgeon with the sling exiting the patient's skin.

86. In Ethicon's Draft GYNECARE Value Proposition Report Project TVTx of November 9, 2004, there is Ethicon's discussion of the development of the TVT-O System:

> *In 2001 Delorme, a French urologist developed a new approach, which involved placing the tape under the mid urethra horizontally through the obturator foramen. The needle passes from the 'outside in' towards the urethra. The procedure was positioned as eliminating the risk of bladder, major vessel and bowel injury in addition to being easier to perform, quicker and no need for cystoscopy. Initially the procedure was perceived with great skepticism due to the concern for damaging the obturator nerves and vessels. With the assistance of cadaver dissections, which demonstrates the distance of around 4 cm- 5cm from such structures surgical approach, has since gained rapid interest.*
>
> *The quality of the clinical publications on the transobturator 'outside in' approach is currently poor and it has become apparent that the risk of bladder perforation has not been totally eliminated as demonstrated in the below references. It is believed that the risk may be higher in patients with prolapse and obesity. Another complication being reported with the 'outside in' transobturator approach is urethral injury.*

[21] ETH.MESH.06705963

GYNECARE TVT Obturator was introduced in January 2004. To date it is now estimated that over 20,000 procedures have been performed worldwide.[22]

87. There was no clinical information about performance or risk provided to the FDA reviewer. Ethicon submitted its new 510(k) (K03368) cleared on December 8, 2003 to begin to market its TVT-O System. The predicate cited by Ethicon for its GYNECARE TVT-O System was Ethicon's GYNECARE TVT System with both cleared for the same intended use, namely treatment of SUI symptoms. However, as not adequately described by Ethicon to an ODE non clinical reviewer, the proposed TVT-O System introduced new issues of safety and effectiveness for the surgeon and the patient including risk of damaging the obturator nerves and vessels. Ethicon's TVT-O changed the recommended insertion approach and technique for the surgeon to 'outside-in'. The same sub-urethral horizontal sling could also be placed as 'inside-out'. Ethicon changed the size of the Prolene sling implanted, the insertion tools and potential risks for the patient from more lateral insertion when compared to prior TVT System. As stated by Ethicon in the 510(k), both implanted as TVM a tension free vaginal Prolene mesh tape for tissue ingrowth and intended for SUI. However, as not adequately described the TVT-O delivered the sling via a new trans-obturator approach using new insertion accessories and raising new potential risks not addressed by Ethicon in the draft IFU. The sling implanted, unlike the TVT's 'U' was now a horizontal "H" (hammock) sub-urethral sling which was shorter and placed closer to the urethra as a 'sub-urethral hammock'. The surgeon inserted the TVT-O sling along a new anatomic route along the patient's posterior ischiopubic ramus and through the obturator membrane. The TVT-O was cleared by FDA as intended to treat SUI.

88. However, unlike the information in the 510(k) claiming substantial equivalence, the TVT-O System was marketed by Ethicon with claims that it provided a 'safer approach' with less risk of vascular injury and potential blood loss than the prior TVT System in terms of the reduced risk of major injuries related to blind insertion of the TVT U shaped sling via a retro-pubic route in the pelvis. There was no clinical data in the TVT-O 510(k) to support that Ethicon's comparative marketing claims that TVT-O as a safer procedure than its TVT System. Such new comparative marketing claims would need scientific support and clearance by FDA. Instead Ethicon's 510(k) submitted to FDA for TVT-O elected to claim only substantial equivalence of TVT-O to the TVT System.

89. Also, not adequately described in the TVT-O approach through the obturator membrane was an increased risk for permanent injury to a patient's leg than the risk for the prior approach used for the TVT System. Ethicon's 510(k) did not include a head to head comparison of the TVT System and TVT-O to support comparative claims for the two products in terms of increased risks or improved effectiveness as treatments for SUI.

90. In Ethicon's Draft GYNECARE Value Proposition Report Project TVTx of November 9, 2004 includes information about Ethicon's marketing of its new TVT-O System:

The main benefits of TVT-O perceived by physicians are as follows:
- *Same Proven mesh*

[22] ETH.MESH.06705963

- *Minimal tissue dissection*
- *Passage away from urethra*

The main product challenges:

- *Winged guide perceived as additional step*
- *Exit of TVT-O needle perceived more lateral*[23]

4. Ethicon's New 'Mini' Single Incision Sling (SIS) "TVT-SECUR" That Ethicon's 510(k) Called 'Substantially Equivalent' to Predicates TVT and TVT-O

91. Relevant to this report is Ethicon's "Next Generation TVT product's 510(k) for marketing 'TVT-SECUR'. Ethicon's strategy to pursue this product was stated in an internal November 30, 2004 "TVT-NEXT (TVTx) Development Contract. In 2004, Ethicon had a dominant role in the SUI Sling market and 91% profitability of its TVT sling kits:

> ***EXECUTIVE SUMMARY***
>
> *...Annual sales of the GYNECARE TVT brand (TVT & TVT O) in the direct markets is estimated to reach $~100MM by end of 2004 with a profitability of ~91%. This high profitability being key to the GYNECARE business as no other product within the pipeline can demonstrate such profitability, which could assist to replace profit from this critical platform....*
>
> *GYNECARE continues to be the market leader in the sub urethral sling market with an estimated market share in US at 46% and 59% European D4. It remains strongly recognized that GYNECARE developed this market and coupled with the skills, competencies and capabilities within the organization such market dominance can be sustained. However, product innovation and advancement is required in order to stay ahead of the competition.* [24]

92. Ethicon described its Strategy for 'TVTx' in December 6, 2004 and why it should pursue development of a new 'mini type' TVT-SECUR project in order to maintain its market leadership:

> *To maintain market leadership in the increasingly competitive surgical SUI market. Market and IP intelligence confirms competitor development plans for "mini type' TVT devices. Based on our experience of the transobturator approach without the launch of TVTx...demonstrates the projected market share in both US and Europe. It is anticipated there will be at least two competitor 'mini type' devices launched in 2006.*[25]
>
> ***Customer needs***
> - *Less invasive than current needle passing techniques*
> - *Reduced operative complications*
> - *Less post-operative pain (leg pain for obturator, abdominal pain)*

[23] ETH.MESH.06705963
[24] ETH.MESH.01217673
[25] ETH.MESH.01217673

- *Reduced operative bleeding and reduced risk of hematoma*
- *Quicker procedure*
- *More tolerable under local anesthetic*
- *May open up customer base to an office based procedure in the long term*
- *Less foreign body due to shorter tape*[26]

93. The December 6, 2004 Draft "GYNECARE Value Proposition TVTx" included the following critical assumptions to guide Ethicon's development of a new TVTx product. One factor was the reliance on subjective 'perception' of physicians for product development in terms of TVT-S' proposed retropubic insertion versus the TVT's suprapublic insertion. Also such a new one incision product would have lower requirements for analgesia for women during implantation:

    1. *Shorter mesh implanted will provide equivalent efficacy compared to current mesh length and position*
    2. *Same inserter tool can be used for both obturator/retropubic approaches.*
    3. *The benefit of TVTx low placement in the retropubic space is perceived as a benefit by existing retropubic physicians*
    4. *Ability to be performed with less analgesia and higher patient tolerability*
    5. *One mesh length will be adequate for all patients*
    6. *Physicians perceive the risk of bladder perforation with retropubic direction to be greatly minimized compared to classic TVT*
    7. *Physician perceive risk of damage to major vessels and organs to with retropubic direction placement to be eliminated compared to classic and suprapubic TVT*
    8. *Physicians perceive a benefit of no adductor mU.S.C.le passage of device and tape for the obturator direction placement compared to TVT-O and other transobturator devices*
    9. *Physicians perceive benefit in damage to the obturator bundle to be greatly minimized with the obturator direction TVTx compared to currently marketed transobturator approaches.* [27]

94. In terms of Ethicon's 2004 "E. Customer Segment Analysis" and the headings 'Unmet Need' for the physicians and current "Challenges/Issues" was placement of a sling in retropubic direction in a patient but without actually entering her pelvic retropubic space:

    Unmet Need
    Minimally invasive procedure for treatment of SUI, which offers high efficacy but reduces morbidity compared to the current needle passing techniques. To have potential ability to be performed under 'true' local anesthesia.

    Challenges/Issues
    - *Short term fixation strength*
    - *A new implanted material (ETHISORB)*

[26] ETH.MESH.01217673
[27] ETH.MESH.06705963

- *Long term efficacy*
- *Confusion on how to determine which placement*
- *Ability to adjust*
- *Retropubic direction placement does enter the retropubic space.*[28]

95. Ethicon's goal for development of TVTx in 2004 was a one-size fits all tape sling. It hoped to create a new surgical procedure for SUI which provided high efficacy for treatment of SUI but had a very low risk of complications, low need for analgesia, when compared to the current gold standard for mesh slings which relied on implantation by needle passing devices. The TVTx with use of inserters would eliminate the needles to be passed through the pelvis. The goal of Ethicon's new inserter was to permit a surgeon to implant its new smaller 'mini' sling facing in a retropubic direction in a patient but without the risks of entering her retropubic space.[29]

a. Ethicon Submitted its TVT-SECUR 510(k)

96. The 510(k) was assigned by FDA K052401 when submitted to FDA on September 1, 2005, with an amendment to the 510(k) submitted November 17, 2005 with additional information and cleared by FDA's General Surgery Devices Branch on November 28, 2005. The submission included a copy of Ethicon's check to FDA for the submission's User Fee of $3,500.00 dated August 25, 2005. [30]

97. Ethicon's Premarket Review Coversheet for the 510(k) indicated that Ethicon cited no standards in its submission, it was a traditional 510(k) for a "modification of existing device." The reviewer was informed that the related 510(k)s for TVT-SECUR for substantial equivalence are: K974098 (TVT), K012628 (TVT) and K033568 (TVT-O). There is no inclusion of the Codman Ethisorb Dura Patch 510(k). The product code for the submission is 79FTL- general surgical mesh as described by 21 C.F.R. § 878.3300, a Class II device. The indications for use are the same as for the cleared TVT System:

> *The GYNECARE TVT SECUR* device is intended for use in women as a sub-urethral sling for the treatment of stress urinary incontinence (SUI) resulting from urethral hypermobility and/or intrinsic sphincter deficiency.*[31]

98. The TVT-SECUR product in the 510(k) was primarily the research and design efforts of Ethicon's Engineer Dan Smith. In an internal 11/2004 'revised 2004' "Strategy Tree Project Definition" with the project name: "Next Generation TVT-X", the project was to be completed by Ethicon's staff and launched in 18 months. The R&D Budget for 2004 had set aside $0.6 MM for the project. The initial discovery phase of the project had been headed by Mike Tracey (R&D Discovery), with completion of the project transferred to Dan Smith, Engineer, R&D.[32] The original Design Validation Protocol for the GYNECARE TVT

[28] ETH.MESH.06705963
[29] ETH.MESH.06705963
[30] ETH.MESH.07876572
[31] ETH.MESH.06705963
[32] ETH.MESH.00259042

SECUR System (TVT SECUR DHF 0000120) (see discussion of Design Validation below) was dated September 20, 2005, after the 510(k) had been submitted to FDA but the Report was dated December 10, 2005, one month after clearance.[33]

99. Ethicon's 510(k) cover letter signed by Patricia Hojnoski, Ethicon Senior Project Manager, Regulatory Affairs, indicated to FDA that the 510(k) was a modification to the GYNECARE Tension-Free Vaginal Tape System (TVT) and the predicates were K033568 (TVT-O), K012628 and K974098 (TVT System). There is no reference to **CODMAN Ethisorb Dura Patch**, or that the absorbable material placed at the ends is cleared as **Vicryl and PDS suture**, and that the ETHISORB DURA PATCH will have a short-term and unstudied role to stabilize the sling in a woman's pelvis before there is tissue ingrowth. The reviewer does not have an adequate description of the difference in the sling size from TVT and TVT-O and will be marketed as a new "**mini**" sling option, when seen by one of Ethicon's TVT experienced surgeon reviewers during Design Validation called "*small/tiny*".[34] The ODE reviewer is not adequately informed by the use "**similar**" just how different the proposed insertion of the TVT SECUR is in terms of a U or H approach, with greatest difficulty experienced in product evaluation with the new U approach. There is also mention of the requirements for "tensioning" of this sling and that internally Ethicon is aware that the TVT SECUR is a unique new device when compared to either of the TVT and TVT-O predicates. Based on a single incision, the FDA is told that the new system is less invasive, but there is no data to support that claim in terms of potential for patient risks or outcome. The modifications to the existing device are described to FDA as follows (underlining added for emphasis):

> *The GYNECARE TVT Universal System is <u>less invasive 'exit less' device</u> that will enable the physician to perform a suburethral sling procedure placing the mesh under the mid urethra without either the delivery device or the implant exiting the skin. The currently marketed TVT device exits through the abdomen or through the thigh. In addition, for TVT SECUR, the delivering device and mesh will have the flexibility to be placed in either a "U" or "Hammock" direction. <u>Both approaches are similar to existing validated techniques;</u> however, the modified device offers a less invasive approach. The "Hammock" approach affixes into the internis mU.S.C.le or into the internis mU.S.C.le and membrane. The "U" approach affixes into the lower edge of the pubic synthesis in the connective tissue of the endopelvic fascia. The placement will depend on surgeon preference and individual requirements of the patient. The placement of the mesh (midurethra) remains unchanged.*
>
> *The ends of the mesh will be sandwiched between layers of absorbable material made from polyglactin 910/polydioxanone fleece material coated with polydioxanone film. The coated ends are added to facilitate passage (stiffens the ends) and placement (tactile feel for the surgeon) of the mesh implant, <u>but are then absorbed leaving the ends ingrown into tissue.</u> Two curved, stainless*

[33] ETH.MESH.05530893
[34] ETH.MESH.05530449

steel, single use introducers are used to deliver the implant. The introducers are supplied fixed to the implant via a wire through the coated ends and inserters.

The GYNECARE TVT SECUR System does not change the intended use of the application of the TVT tape.

QUESTION

Does the submission include clinical information? - No[35]

100. Section 5 of the 510(k) is the 510(k) Summary, also with reference to Ms. Hojnoski, who again not adequately inform the FDA that there is a significant change in the method of operation for the surgeon to implant the device and the size (8cm) and elasticity of the sling implanted in a patient compared to TVT products, untested holding forces for Ethisorb Dura Patch in the pelvis, change to laser cutting of the mesh, raising new issues of safety and effectiveness. Instead, the FDA is told that the device "meets the established performance requirements" but with no statement that would include a safe and effective device for permanent implantation in a patient. The conclusion implies – but does not state- there are no new and unaddressed issues of safety and effectiveness which have not already been seen in the TVT or TVT-O predicates:

Technological Characteristics:

The modified device has the same technological characteristics as the predicate device. The form, fit, function and method of operation are similar.

Performance Data:

Results of verification testing indicates that the product meets the established performance requirements.

Conclusion

Based upon the 510(k) summaries and 510(k) statements (21 C.F.R. 807) and the information provided herein, we conclude that the subject device is substantially equivalent to the predicate devices under the Federal Food, Drug and Cosmetic Act.[36]

101. Section 6 is Ethicon's "Truthful and Accuracy Statement" which is required by 21 C.F.R. § 807.87(k) to be in the 510(k) submission. Ethicon's statement was signed by Patricia M. Hojnoski and dated August 30, 2005. The presence of this signed statement from Ethicon, the knowledgeable expert for the product, supports for FDA's ODE reviewers it can trust the quality and accuracy of the information provided to the agency in the 510(k). Ethicon has assured the FDA that its 510(k) is truthful, accurate and that "no material fact has been omitted". This statement must be signed by an employee of Ethicon and it cannot be signed by an outside consultant. To provide a false certification or to leave out 'material facts' about the product or products in general from the 510(k) becomes a crime against the

[35] ETH.MESH.07876572
[36] ETH.MESH.07876572

Federal government, a violation of the Act and as such immediately misbrands the related medical device described in the 510(k).[37]

102. Without the presence of an Ethicon signed Truthful and Accuracy Statement, an Ethicon 510(k) application cannot be even filed by FDA to begin reviewing the submission. The FDA's reviewer in ODE's surgical devices branch, assigned the task to complete a 510(k) submission review within 90 days, must rely on Ethicon's Truthful and Accuracy certification, as well as Ethicon's knowledge and experience as the expert and designer of TVT-SECUR and other similar products, including the TVT predicates and CODMAN Ethisorb DURA PATCH to be willing and able to provide FDA with adequate and complete disclosure about the device it intends to market. FDA must assume that Ethicon intends to sell a safe and effective product for implantation in patients in the United States.

103. The FDA reviewer is also aware that it is a Prohibited Act (21 U.S.C. § 331(a)(b)) for Ethicon to sell a medical device in the United States that is not safe, effective and adequately labeled. As part of the 510(k) process, Ethicon's commitment to adherence to Quality Systems[38] must only be assumed by FDA's ODE reviewer, since that information is not required to be provided by Ethicon in the 510(k), nor is it required to be reviewed or verified at time of FDA's review of the 510(k). Therefore, despite obtaining 510(k) clearance from FDA, it remains Ethicon's non-delegable duty (not the FDA's) to ensure the device it manufactures and commercially markets actually performs as described to FDA and was cleared by its 510(k) when implanted in a patient. It is Ethicon's role (not the FDA's) to ensure that there are no new unaddressed issues of safety and effectiveness for the commercial product which would render its product adulterated and misbranded.

104. Ethicon and Ms. Hojnoski in August 2005 had modified the required Truthful and Accuracy Statement without prior discussion with the FDA reviewer. The known process at the FDA is for the FDA's reviewer to use a checklist to ensure a signed Truthful and Accurate Statement is present in a 510(k) submission. The process at FDA is not to verify the wording or question the intent of the company when it significantly modifies the wording. The FDA's premarket notification 'Truthful and Accurate Statement' for a 510(k) as required by 21 C.F.R. § 807.87(k):

> *I certify that, in my capacity as (the position held in the company) of (company name), I believe to the best of my knowledge, that all data and information submitted in the premarket notification are truthful and accurate and that no material fact has been omitted.*

105. However, Ms. Hojnoski's certification included additional qualifiers and limitations as to the truthfulness and accuracy of the information in the Ethicon 510(k) signed statement. Ethicon has not signed that it has not left out 'material facts' about the product or product like it, only that Ethicon has at some level made a determination that it has not "knowingly" left out material facts related the FDA's review of substantial equivalence for

[37] 21 C.F.R. § 807.87(k); 21 U.S.C. § 352(t); 21 U.S.C. § 331(a)(b); 18 U.S.C. § 1001
[38] 21 C.F.R. § 820

its 510(k). The qualifiers limit the responsibility of both Ms. Hojnoski and Ethicon in its duty to provide material fact to FDA in the submission:

> *Pursuant to 21 C.F.R. 807.87(k), I, Patricia Hojnoski, certify to the best of my knowledge and belief and based upon the data and information submitted to me in the course of my responsibilities as Senior Project Manager, Regulatory Affairs of ETHICON, Inc., a Johnson & Johnson company and in reliance thereupon, the data and information submitted in this premarket notification are truthful and accurate and that no facts material to a review of the substantial equivalence of this device have been knowingly omitted from this submission.*[39]

106. Section 11 MODIFIED DEVICE DESCRIPTION begins Ethicon's description of the physical modified device. Again there is no comparison to the changes in tape length from the predicates, with Ethicon making the claim it is "less invasive," a claim it knew FDA would allow without data for a single incision exit less implant. The description included that the modification of the tape does not change the intended use of the application of TVT tape, however Ethicon did not address that the modification to the smaller tape did change risks in terms of forces on the tape, the changes produced by laser cutting, and elasticity.

107. On the 510(k) submission's page 000028 is a reference to the changes at the ends of the tape. There is mention that the absorbable material is VICRYL and PDS. Ethisorb is called a fleece that is contained in "Codman ETHISORB Dura Patch" cleared as K991413. VICRYL suture is listed as approved as N17-482 and cleared as K946271 and PDS suture is approved as N18-331. Both Vicryl and PDS suture were originally NDA approved as drugs before 1976 and transitioned to medical device regulations. (The "N" is from New Drug Application (NDA) approval for Ethicon). There is no discussion for the Surgical Device Branch reviewer that an additional PDS film has been placed on one surface of Ethisorb Dura Patch to stop passage of CSF fluid out from the brain through the dural patch, basically making the outer patch fluid resistant (waterproof) with the PDS film. Ethicon proposes to continue the PDS film on one surface of the ETHISORB Dura Patch end. The reduced fluid flow (and cell flow) through the tape until the PDS is absorbed could be significant for delaying successful tissue ingrowth into the Prolene mesh tape. It could also hinder tissue ongrowth for the fleece for a TVM tape. Ethicon performed no animal studies, which were designed to simulate forces on the implanted tape as a bladder sling, so the changes in tissue ingrowth for the sling with Ethisorb Dura Patch at the ends of the mini sling were not investigated. The FDA is not told that Ethicon has determined that the fleece and the related 'pore size' and ability for cells to enter the fleece through the PDS film will facilitate tissue ingrowth. It does not discuss the application of the PDS film, which is appropriate for the Dura Patch to prevent leakage of CSF but does not seem to be necessary or to provide a benefit for the proposed use in the Prolene sling. Instead of addressing this new efficacy issue, the FDA was provided the following description with a nonspecific reference to "*pore*" size for the fleece. Pore size is known to be important to tissue ingrowth for synthetic surgical mesh permitting cells for tissue growth access to mesh pores. However,

[39] ETH.MESH.07876572

those tissue forming cells arrive at the mesh pore (even for fleece) for tissue ingrowth by the body's own fluid flow.

108. There is an undated Ethicon PowerPoint presentation titled "Innovation in Mesh Development" by Boris Batke, Associate Director R&D, which provided an overview of mesh and porosity.[40]

> ***Polypropylene Mesh***
> •*Small pore size (<1mm)*
> •*High tensile strength*
> •*Inert and biocompatible*
> •*Resistant to infection*
> •*Inexpensive*
> •*Long track history.*
> *BUT: Small pore size led to high mesh contraction*[41]

109. The problem with heavyweight small pore mesh is that the formation of connective tissue correlates with degree of inflammation but does not correlate with strength. Traditional polypropylene mesh like Prolene or Marlex are called heavyweight (95 $g/m^{2)}$ meshes.[42] There is an increased inflammatory response and scar formation. Before Ethicon shifted to marketing lightweight mesh, GYNECARE marketed softer mid-weight "Gynemesh Prolene Soft (PS)" with a weight 44 g/m^2, pore size 2.44mm processed with heat to feel softer to physicians.[43] Eventually no support for improved benefit. In terms of the hernia repair medical literature, primarily coming from Germany, physicians then began to shift preference to lightweight mesh. Lightweight mesh was made of thinner fibers and knitted with larger pores (spaces- macroporous). Ethicon then began making lightweight mesh but adding absorbable material (from its approved/cleared absorbable sutures) (MPPAM-Macroporous partially absorbable mesh). According to Ethicon's marketing, once the absorbable material was "absorbed" the lightweight underlying polypropylene mesh, would become even lighter weight mesh implanted in the patient over time. It was assumed it would produce a clinical benefit, but not scientifically supported. There were also known risks identified for lightweight mesh such as the increased risk of folding, bunching, rippling, shrinking and loss of strength.

110. Under the Ethicon slide titled **"Macroporous Mesh"** heavyweight mesh, or traditional weight mesh had a 0.8mm pore size but with the fabric fiber bundles knitted close together.[44] In contrast the lightweight or "physiologic" weight mesh had a pore size of 04.0mm Pore size with wide spaces occurring between the fibers. The light weight mesh was constructed of thinner diameter filaments with wider spaces (macroporous). The theoretical advantage of a surgeon using a "light weight mesh" was less risk of implanting foreign body (material) in a patient. For the TVT-SECUR, Ethicon wanted it to be

[40] ETH.MESH.04037091
[41] ETH.MESH.04037091
[42] ETH.MESH.04037091
[43] ETH.MESH.04037091
[44] ETH.MESH.04037091

considered a composite "lightweight mesh"- made of thin polypropylene fibers knitted into wide open spaces (pores) 'macroporous' as a 'fleece' containing partially absorbable material (Vicryl/PDS). The absorbance of the Vicryl and the PDS component out of the ETHISORB fleece and the underlying Prolene mesh sling tissue ingrowth would theoretically lessen the total bioburden of implanted material in a patient over time but provide the opportunity for tissue ingrowth and sufficient strength (greater strength is thought due to the increased production of collagen). Mesh with larger pores are to have less bridging fibrosis than small pores, with lightweight 3.5-4.0 pore sizes compared to Midweight mesh with pore size of 2.4mm.[45] However, the time for absorption of the suture material is usually based on data from its use as an implanted suture for ligation or holding tissues. It is not calculated in terms of total absorption of a larger surface area of exposure.

111. Another example of Ethicon's use of composite mesh strategy consisting of a polypropylene mesh intended as a TVM pelvic floor repair (PFR) for pelvic organ prolapse (POP) Prolift +M System. The Prolift+M System uses Ethicon's cleared UltraPro Mesh + the "M" component Monocryl (poliglecaparone-25). The absorbable material was cleared as suture (like both Vicryl and PDS). Ethicon first obtained clearance of this combination as a general surgical mesh called UltraPro (mesh weight 28 g/m^2, pore with Monocryl absorbed 4.0mm).[46] The ultimate goal of Ethicon's use of composite fabric (mesh + absorbable suture material) was to produce a milder inflammatory reaction, good tissue integration and minimal scar. Another example of an Ethicon product is Gynemesh M-Mesh which is Prolene + Monocryl, (thin monofilament fibers with large pore size filled with Monocryl absorbable material). The additional absorbable component is to be slowly absorbed by the body and help reduce the early phase inflammatory reaction after the mesh is implanted. It is also not to negatively impact tissue ingrowth. However, the evolution of surgical mesh has been in the abdomen and groin and not the female pelvic floor. The environment of the pelvis and stresses of movement, including sexual activity, are different in the female than the abdomen and groin.

112. Ethicon's PowerPoint described the recognized failure modes for mesh: Extrinsic- constant, static load (caused by organ weight); dynamics load (caused by one-time action like coughing); and oscillating load, much less magnitude than breaking load. The Intrinsic cause for mesh failure was stress concentration. "Increased stiffness of a prosthetic device has been associated with an increased rate of complications in multiple biological systems."[47] Gynemesh PS stiffness<< than UltraPro/M Mesh "Absorbed."[48]

113. Ethicon's proposed design taken directly from the Codman Ethisorb Dural Patch has appeared to also potentially block the passage of fluid with cells into the ends of the mesh sling by the manufacturing addition of PDS film bonded thermally to the fleece and mesh. Thermal bonding melts the PDS and Vicryl resin (plastic) as well as the polypropylene Prolene mesh, further reducing the ability of fluid to flow through the ends of the mesh tape also reducing entry of fluid with cells into the mesh pores for tissue ingrowth. Ethicon says

[45] ETH.MESH.04037091
[46] ETH.MESH.04037091
[47] ETH.MESH.04037091
[48] ETH.MESH.04037091

to FDA the pore size is "sufficient" but does not provide any data to support that it has determined or conducted any pre-clinical studies with TVT-SECUR to determine that the pore size as proposed and physically available to the cells "*permitted continuing growth of cells and intrinsic body tissue*" or if this information was taken directly from the pre-clinical studies in the sutured Codman Ethisorb Dura Patch 510(k) for a completely different use in the dura where PDS film was applied to only one surface of the Ethisorb to prevent loss of CSF while the uncoated fleece side permitted tissue ongrowth:

> *The fleece sandwich is a synthetic absorbable composite material made from VICRYL and PDS yarn. The yarn is knitted, processed into a fleece layer, the layers are then sandwiched to the mesh by using two pieces of dyed poly-p-dioxanone film using a thermal process. The resultant fleece material is of sufficient pore size to allow continuing growth of cells and intrinsic body tissue…Absorption of sandwiched fleece ends is essentially complete within approximately 90 days, the fleece layers are replaced as connective tissue grows into mesh Portions of the PDS yarn/fil can be detected up to 180 days post-implantation.*[49]
>
> *Two curved stainless steel Inserters are provided to deliver the implant that is secured to the Inserter by release wire. The release wires are secured to the inserter by the finger pads. The protective cover is used to cover the 2nd inserter tip and is removed before insertion. A standard needle holder attached to the Inserter delivers the implant. The Inserter allows for common surgical instruments to aid in the smooth and consistent placement of the implant.*[50]

114. Section 12 is the Substantial Equivalence discussion with a table for comparison of predicates TVT and TVT-O with TVT-SECUR. For the 'implant device', FDA (unlike Ethicon's marketing) is told that both TVT and TVT-SECUR both have "*stainless steel needles attached to each end of the mesh.*" There is a later reference to the "Inserter" but as an Accessory. TVT accessories are: TVT Introducer, TVT Rigid Catheter Guide, TVT Abdominal Guides and Couplers. For TVT SECUR accessories are: Stainless steel inserters that are supplied attached, then removed and discarded after implant. For the length of tape- TVT has ~500mm, TVT-O ~450mm and TVT-SECUR ~80mm. For TVT and TVT-O - a portion is cut off and discarded after passage. There is no discussion in the comparison of the predicates for SE of the manufacturing change to cut the mesh by laser with thermal edge changes from either of the predicates, and for a product requesting to be cleared as a surgical mesh, the change in the elasticity of the mesh sling. [51]

115. Ethicon provides no follow-up discussion of the significance of the changes in the sling tape implanted in the patient, potential for tissue trauma from the use of a laser cut edge, the change in elasticity and the differences in anatomic forces placed on the tapes and potential changes in outcome of treatment of SUI between TVT, TVT-O and TVT-SECUR. The table included "mm" rather than tape as cm- TVT 50 cm, TVT-O 45 cm versus TVT-

[49] ETH.MESH.07876572
[50] ETH.MESH.07876572
[51] ETH.MESH.07876572

SECUR 8 cm. The significance of the change in the sling tape size is more recognizable using cm versus mm.

116. Ethicon concluded for FDA Section 12 with the following statement:

> *The GYNECARE TVT SECUR System does not change the intended use or the application of the TVT tape.*[52]

117. This is a misleading and inaccurate statement. Ethicon knew internally there was significant change in the "application" of the tape, when 'application' refers to the actual applying or "implantation" of the tape by the surgeon.

118. That is the extent of the discussion of the comparison of TVT-SECUR to the predicates other than an additional statement that the "GYNECARE TVT Universal System" is less invasive 'exit less' device that will enable the physician to perform a sub-urethral sling procedure placing the mesh under the mid urethra without either the delivery device or the implant exiting the skin. Again no data to support that the device is actually "less invasive " for a patient and will result in either equivalent or improved clinical benefit for treatment of SUI. There is no comparison for the ODE reviewer of the risks and differences of the surgical procedures for implantation of TVT as a "U" and TVT-O as an "H" in terms of the new requirements for the surgeon for TVT-SECUR (Universal) for either "U" or "H" approach. There is no discussion of "tensioning" for TVT-SECUR compared to the cited predicates.

119. Section 15 is Biocompatibility and is actually a letter from Ethicon Products Worldwide sent to Patricia Hojnoski from Dr. Joerg Holste, Research Fellow, Preclinical Safety Evaluation Corporate Product Characterization Ethicon R&D Europe dated August 18, 2005. The letter provided a general overview of the history of Ethisorb Dura Patch and Prolene. The Ethisorb discussion references pre-clinical testing performed for clearance of the dura patch indication (not TVM bladder sling). As part of the Least Burdensome methods for industry, the history of the prior clearances as well as approvals for these materials can be bridged (cited) by Ethicon to prevent its having to conduct duplicative biocompatibility testing for TVT-SECUR.

120. Regarding TVT-SECUR biocompatibility there is one pre-clinical animal study provided in the letter. It was a Non-GLP[53] peri-vaginal implantation in sheep pelvic tissue of representative GYNECARE TVT SECUR Implants over 12 weeks. The results indicated that this PROLENE Mesh and polyglactin 910/polydioxanone fleece material coated with polydioxanone film was well tolerated and without adverse effects. The polyglactin 910/polydioxanone fleece material coated with polydioxanone film of the implants was essentially absorbed between 4 and 12 weeks. The letter does not specifically state that the testing was performed to investigate (simulate) the intended use of Ethisorb Dural Patch

[52] ETH.MESH.07876572

[53] Non-GLP= non Good Laboratory Practices, therefore the laboratory study was not performed consistent with recognized good laboratory practices and as described in 21 C.F.R. § 58.

with Prolene for design as a TVM bladder sling in any animal model, only that it was well tolerated.[54]

121. Section 18 called "Performance Testing: Bench" Ethicon indicated that there was no bench testing provided in the 510(k). Incredibly, Ethicon did not provide any bench testing to the FDA despite the significant changes to the TVT SECUR including the forces placed on the mesh, the design of the inserters when compared to the predicates. There was no bench testing of the changes to the mesh tape despite clearance as a surgical mesh in terms of introduction of laser cutting of the mesh, thermal changes, changes to patient tissues from laser cutting and mesh elasticity.[55]

122. Section 19 of the 510(k) was Performance testing: Animal and Human Cadaver. The overall summary for the FDA reviewer was that Ethicon provided:

> *Summary of: A 3 month Pre-Clinical trial to Assess the Fixation Force of a new TVT (TVTx) in the Sheep Model (Ethicon Study No. SO04/2-21)*
>
> *Summary of: Evaluation of Fixation Force for the GYNECARE TVT-SECUR Device in a Sheep Cadaver Pelvic Floor Model (PSE Accession Number 05-0395, Project Number 67379)*
>
> *Summary of: Evaluation of the Pullout Force of GYNECARE TVT SECUR Implanted into the Urogenital Diaphragm and Obturator Membrane of a Human Cadaver (PSE Accession Number 05-0396, Project Number 67379).*

123. The sheep study, as titled appeared to address the proposed use of the TVT-SECUR in a sheep model. No photos or drawings were included in the protocol discussion or the FDA reviewer. However, according to the protocol, it was not designed to look at fixation force for the TVT-SECUR tape in a clinically meaningful way as to how it was intended to be implanted in a woman. Multiple patches were implanted in the sheep with no additional force or pressure to look for evidence of absorption. The summary of the acceptability of the findings of the sheep study are signed by Dan Smith, Project Leader on August 25, 2005. Dan Smith is an engineer and would not be the appropriate individual to provide meaningful discussion of the outcome of the pre-clinical sheep study findings. There is no other signature on the sheep study for the TVT-SECUR other than Dan Smith.

124. The other two cadaver studies, also would have no immediate relevance to a living woman and use of the product in the pelvis for the U and H technique approaches. Both of the cadaver studies are listed as part of the same Project Number 67379. There is no Ethicon employee signature for either of the two cadaver studies. So in Section 19, the Performance Section the only Ethicon individual identified as involved to determine satisfactory performance is Dan Smith.[56]

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125. Section 20 is Performance Testing: Clinical with Ethicon indicating the section is not applicable, "since clinical data was not required to support this submission." [57]

126. Dr. Lerner, a Medical Officer in DGRND/PRSB (ODE's Supervisory Medical Officer /Plastic and Reconstructive Surgery Branch) was assigned Ethicon's TVT-SECUR 510(k) by Division to review for clearance. He obtained another medical officer consult from urologist Hector Herrera, MD, medical officer DRARD/ODE/ULDB (ODE's Urology Lithotripsy Devices Branch). That consult is dated September 22, 2005, and Dr. Herrera wrote about his clinical concerns for the proposed device including that the length of the tape was too short and there needed to be follow-up for 12 months to ensure it was effective, there were issues of tensioning and he looked at the difference in description of the predicates with "bi-directional elasticity." Dr. Herrera as a CDRH ODE urologist was able to see that there was a fundamental change in the surgical technique proposed for treatment of SUI. Based on the significance of the proposed changes in the surgical technique and device he thought that Ethicon should use a different predicate than TVT or TVT-O. These are the same types of issues which should have been foreseeable to the product experts at Ethicon, but which they failed to adequately address:

> *The total length of the tape is only 8 cm, if we assume that the area below the mid urethra is 2cm, that leaves only 3cm of tape at each side, would this very short arms produce a hammock or "U" effect, and would this short arms be retained by the tissues and produce a meaningful clinical effect elevating the urethra?*
>
> *I do not think so; the degree of sling tension that is required to achieve continence is different in different type of patients and depends on the length of the tape, the tension of the suture, or the tension of the tissues in the "tension free" tapes.*
>
> *The mesh as labeled in other submissions, reads: "is designed to have bi-directional elasticity to allow adaptation to the various stresses encountered when placed as a urethral "backstop" to treat stress urinary incontinence."*
>
> *Would the very short arms, of the proposed device accomplish this effect? I do not think so; there is not enough length on the present tape for the tissues to exercise tension on only 3 centimeters.*
>
> *The present 510(k) submission presents a fundamental change in the state of the art surgical technique for sling treatment of urinary stress incontinence. The company has not provided evidence to support this use.*
>
> ***Recommendation***
>
> *I do not know of any validated technique for this new approach as far as safety or effectiveness is concern.*

[57] ETH.MESH.07876572

> *The company should use as a predicate a device that uses exactly the same surgical approach otherwise performance data and clinical outcomes about the implant technique will be needed. Patients would have to be follow-up for at least 12 months, because the device may be retained well for a few weeks and later show the real effectiveness.*

127. Dr. Lerner then wrote a September 23, 2005 510(k) Memorandum to the record. His point 2 is a discussion titled "Comparison of the Technological Characteristics (Design materials, Sizes, Features, Shapes, etc.) of the Subject Device and Predicate(s)" he included that Dr. Herrera of DRARD/ULDB recommended Ethicon obtain clinical data to support changes in the product. So Dr. Lerner was aware on September 23 that the new tape was short, that the length was a concern to Dr. Herrera, a urologist, as well as the change in the elasticity of the mesh and the potential lack of providing adequate tension to treat SUI:

> *Dr. Hector Herrera of DRARD/ULDB has reviewed this submission, and he feels that the length of the tape (8cm) and the mechanism of insertion are different from the predicate devices, and that the bi-directional elasticity to allow adaptation to various stresses encountered when placed as a urethral "Backstop" to treat incontinence would not be enough to exercise tension n only 3cm of mesh per side. Therefore, he wants clinical data to support this new approach for this mesh (See attached memo for Dr. Herrera.*[58]

128. Dr. Herrera nor a CDRH toxicologist had addressed the change in the Ethisorb Dura Patch for the new indication proposed by Ethicon. There was no consult by Dr. Lerner with a member of ODE's Neurology devices Branch about the clearance history of ETHISORB Dura patch and the proposed change in its use as a TVM SUI product.

129. Based on Ethicon's Section 15, Dr. Lerner thought the Biocompatibility testing was adequate. He noted the sheep study demonstrated the device is not-cytotoxic, without adverse intracutaneous activity, and non-pyrogenic. "Taken as a whole, there is adequate data to support biocompatibility equivalence."[59] However, Ethicon was referencing use of materials with long history as permanent implants, so Biocompatibility would not be a major issue.

130. Regarding the Effectiveness Data- Subject Device, he once again mentioned the sheep studies as having been performed on the evolving design of the TVT. He indicated that the third sheep study (a cadaver study) was designed to address the holding power of the tape after improvement in the sandwich fibers at the end of the tape, and design change of the tape. "*This study did confirm that the device had adequate holding power in this sheep model: Using 80-160 lb. cadavers, the device was positioned, repositioned, or reinserted, and it was demonstrated that the device would hold in place*." [60]

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131. Dr. Lerner indicated that the second sheep study was performed to assess the fixation force of the TVT. Eight sheep were used (1, 2, 4, 12 weeks) n=2 in each group, with the primary objective to demonstrate that the fixation of the SECUR tape in a sheep over time is equal or better than standard TVT product; the secondary objective was to assess the fixation force of the SECUR at different times was at least the same as the original TVT mesh. These objectives were met. There is no mention that Dr. Lerner was aware that the model in the sheep did not simulate the required stresses on the tape in a living implanted patient or that there were differences in the initial fixation of the TVT predicates and TVT-SECUR slings also not simulated in the sheep study protocol.

132. His discussion continued to reference Dr. Herrera and that the effectiveness data was reviewed by Dr. Herrera from DRARD and he recommends a clinical trial with 12 months of follow-up data based on the potential differences in TVT-SECUR when compared to predicates and the inadequacies of the sheep studies (living and cadaver) in relationship to the proposed use in a woman for SUI:

> *...and he believes that these results do not adequately address the human model and that he is concerned the length of the mesh extending out from both sides after placing under the urethra will not allow adequate fixation and support over a period of time. The main difference between this device and predicates is that the mesh extending from beneath the urethra in other tape systems is secures(sic) to the pubic area, thus maintaining the angle of correction at the urethra for control of stress urinary incontinence. Dr. Herrera is concerned that the 2-3 cm mesh which is to become "fixed" in the pelvic soft tissue (as there is no fixation to the pubis) will not be of adequate length. He does not feel the sheep models presented adequately demonstrate the effectiveness of the device over a long period of time, and there are certainly different physiological characteristics between the sheep and human (posture, stress with voiding, etc.). therefore, he recommends a clinical trial with a 12 month follow-up. See his attached memo.* [61]

b. Ethicon Received FDA'S Request for Additional Information (AI) on October 4, 2005 including a Clinical Trial with 12 Month Follow-Up

133. FDA sent an Additional Information (AI) letter to Ethicon on October 4, 2005.The letter was signed by Mark Melkerson, Acting Director, Division of General, Restorative, and Neurological Devices. Questions on the content of the letter were to be sent to Herbert Lerner, M.D. The information was called necessary for FDA to complete the 510(k) review. The FDA's first question was regarding Ethicon's use of pre-clinical animal studies and cadaver models to support the adequate "holding power" of the TVT SECUR in the pelvis. The FDA's wrote to Ethicon for information about the new product design and ability to remain implanted in the pelvis and need to have clinical data to address new issue of performance raised by the design:

[61] ETH.MESH.07876572

Physiologic challenges in the human female are quite different than the animal data you have presented, and that the new characteristics of the TVT (8 cm length of mesh with "wings" of 2-3 cm. beyond the urethra on each side) provide new concerns for the effectiveness of your device. Please provide clinical data to support the effectiveness of this device. This data should include 12 month follow-up to address our concerns regarding the characteristics of the device.

You indicate, in Section 18 of the submission, that bench testing was not provided for this 510(k). FDA feels that, because of the "construction" of this device, this testing is necessary....

You indicate, in section 15 of the submission, that the biocompatibility risk assessment is a compellation of data from predicate devices and other cleared medical devices such as the Codman ETHISORB Dura Patch. Please provide:

○The complete 12 week sheep peri-vaginal implant report with the associated histological evaluation...[62]

134. Ethicon's Martin Weisberg, M.D., Senior Medical Director, Ethicon, Inc. sent a response to FDA on October 25, 2005 directed to Dr. Lerner. It also sent a copy of the response directly to Dr. Herrera. Ethicon's response was that it disagreed with FDA request that it needed to obtain clinical data. The rationale provided by Ethicon was that it had supported clearance based on sheep and cadaver work. However, even more important from a regulatory point of view and what FDA is capable of requesting from industry as the Least Burdensome Methods if that Ethicon identified an additional new 'cleared' predicate to support clearance of TVT-SECUR, namely predicate **"Gyne Ideas Mini Tape". Identification of a cleared predicate mini tape device would make it virtually impossible for FDA's ODE reviewers to now request a 12 month clinical trial from Ethicon when none was requested of Gyne Ideas for clearance of a mini tape for SUI:**

....substantial equivalence to the existing TVT device through extensive sheep and cadaver work. The fixation force studies in the human cadaver tissue, both for the "U" and "Hammock" procedure, showed similar results into the sheep fixation data. In our "Summary of sheep and human cadaver labs..."we describe how the 8cm length was decided upon, and through our cadaver labs and attached diagrams we illustrate how this length is sufficient for the female anatomy.

We would like to offer that if you have additional concerns regarding TVT SECUR, you may contact Scott Serels M.D. Dr. Serels is not an Ethicon employee; however, he was a key consultant on the research and development of this product...

[62] ETH.MESH.07876577 in 510(k) ETH.MESH.07876572

We believe that the additional information provided in this response supports the substantial equivalence of TVT SECUR to the currently marketed TVT device and the ***Gyne Ideas Mini tape.***[63]

135. In response to FDA's request for information about the lack of mesh bench testing for TVT-SECUR, Ethicon indicated it did not need to provide new bench testing for TVT-SECUR but was able to reference K012628 for TVT to cite the characteristics of the TVT Blue Mesh. However, Ethicon failed to address for Dr. Lerner there was a regulatory and safety need based on the "Guidance for the Preparation of a Premarket Notification Application for a Surgical Mesh" for additional bench testing based on a significant manufacturing changes such as moving from a long Prolene tape strip mechanically cut to a laser cut TVT-SECUR with ETHISORB DURA PATCH thermally applied with a PDS film at the ends. That change in manufacturing should have required Ethicon to provide additional bench testing and characterization of its 8 cm sling based on changes for the patient and changes in the elasticity of the mesh. Therefore, Ethicon's statement to the FDA and Dr. Lerner was misleading and inadequate disclosure of material fact by Ethicon.

136. Ethicon provided a copy of the Sheep study that was directed by Dr. Rezapour conducted at Assist Medical Sweden, Almunge, Sweden. The study began on May 3, 2004 and ended on July 30, 2004. Eight female sheep were scheduled to be implanted with TVTx (half implant: mesh with one side Ethisorb coated[64] that were inserted vaginally at the level of the mid urethral in the left and right paraurethral canal (4 samples each side) into the retropubic area of each sheep. At each experimental time point (1, 2, 4, and 12 weeks) after collection of the implanted TVTx samples, at least one additional standard TVT tape was implanted using standard TVT procedure and tested for pull out force. This one standard TVT sample acted as a baseline (control) for each specific time point. [65] There was no simulation in the sheep of the placement of a TVT-SECUR design mini sling or the forces that would be placed on a mini sling. The primary measurement was the pull out force of the mesh strip. In this population of sheep, only seven were implanted with one sheep having a bladder perforation (7/409), one minor hematoma (4/406) and one sheep was accidentally dissected before any strips were implanted. The destruction of the implanted mesh was seen to increase after one week in tissue with the destruction of mesh increasing in the following weeks.

137. The fixation force of all TVTx at any experiment time point was greater than the mean initial fixation force of standard TVT. Histology showed no collagen formation or scar tissue at the Prolene tape and no absorption of ETHISORB after 1 week. At 2 weeks after implantation 80% of ETHISORB remained with good tissue integration in the PP mesh. At 4 weeks, 50% of ETHISORB was gone. At 12 weeks there was no ETHISORB present. A further series of 4 sheep samples were embedded in resin (standard for hard tissue like bone). The fixation and dehydration of the samples was insufficient. The samples could not be evaluated.

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[63] ETH.MESH.07876572

[64] Note that the Ethisorb was coated only on one side of the polypropylene mesh- much as in Ethisorb Dura Patch. The mesh was not sandwiched between Ethisorb and then thermally coated with PDS film as in TVT-SECUR.

[65] ETH.MESH.07876572

138. At week 2 mesh tape came out, when it was pulled to a thin rope. (i.e. force-stretch as would occur when implanted as a sling in a woman) .

139. The investigators' "**Discussion**":

> *The aim of this study was to prove the fixation force of TVTx in the sheep model will be equal or better than standard TVT...*
>
> *The holding force of the Ethisorb tip of TVTx exceeded the tensile strength of the PP-Mesh so much, that the elongation of the pulled out meshes even after 1 week in tissue larger than 30%. That implies in our opinion a loss of function of the sub-urethral sling...*
>
> *Although there are differences in sheep regarding anatomy and physiology (i.e. higher body temperature and metabolism in sheep) in our opinion the proof of concept of TVTx was achieved in our animal model with this data.*
>
> *Nevertheless, since the sheep is not identical to humans regarding the size and the anatomy of subpubic area, these results do not apply fully to humans.*
>
> *Conclusions*
>
> *The data collected in this study show the proof of principle of TVTx and could support the realization of using TVTx in clinical trials.*[66]

c. Ethicon Identified "Gyne Ideas Mini Tape" as a Predicate for TVT-SECUR Mini Sling Clearance.

140. Ethicon attached the 510(k) Summary of Safety and Effectiveness for Gyne Ideas Ltd K023898 cleared June 18, 2003. There is no discussion of the commercial marketing of the product in the United States. Gyne Ideas is based in Glascow, UK. The contact person in the United States was Louis Mazzarese. The 510(k) was prepared November 20, 2002 for a polymeric surgical mesh urethral sling. The predicate devices included TVT (K974098), BioSling (K010553), SAFRY Sling (K020007), Surgical mesh Boston Scientific (K020110), T-Sling (K020652), SiiS#1 Tissue Suspension System (K020705), SPARC Sling System (American medical Systems)(K021263)

141. The description of the device was as a polypropylene sling with integral serrated anchoring arms. The sling had an overall length of only 14 cm. It was supplied with two metal needles to aid in the surgical placement of the device.

142. The device had been subjected to in-vitro and in-vivo testing which demonstrated the ability of the device to adequately restrain urethral tissue under conditions in excess of those encountered during normal clinical use.

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[66] ETH.MESH.07876572

143. Intended use was as a pubourethral sling for the treatment of female urinary incontinence resulting from urethral hypermobility and/or intrinsic sphincter deficiency.

144. According to the FDA's 510(k), The Gyne Ideas Mini Tape was cleared by the Division of General, Restorative and Neurological Devices, the same Division now reviewing TVT-SECUR. However, there was no evidence that any clinical review was obtained from a member of ULDB including Dr. Herrera before clearance in 2003. There was some room to require in vitro and in vivo data, but in vivo in the sheep model had been submitted by Ethicon.

145. Ethicon's response to FDA also included an "Expert Opinion form TVT Obturator inventor and confirmation of the IFU (using the final design). One lab was conducted per the IFU and documented with Professor J. DeLeval from Belgium, inventor of GYNECARE's TVT Obturator device and his anatomist Dr. P. Bonnet to look at the TVT SECUR design and anatomical perspective. There was surgeon input with finalization of the IFU with one lab conducted with GYNECARE's own Medical Director Dr. C. Owens to confirm the design and that the proposed device could be used as a universal device. Three additional labs were conducted by two surgeons, Dr. R. Rodgers did two labs and Dr. C. Haynes did the other. The labs confirmed that the TVT-SECUR functioned as expected. It is interesting that none of these surgeons are listed as surgeons in Ethicon's Design validation Studies in September 2005 through December 2005.

146. However, missing from Ethicon's response to the FDA was the results of the cadaver surgeon labs for studies on September 21, 22 and 27, 2005 intended for Device Design Validation. Ethicon did not give FDA a description of the difficulties reported with the device, particularly for the U approach, including bladder perforation, difficulties with the inserter, inadvertent removal of the sling along with the inserter occurring in surgeons experienced with TVT and chosen by Ethicon.

147. Regarding the identification of the predicate to permit clearance of the TVT-SECUR 510(k) despite its potential risks. Before 510(k) clearance on November 28, 2005, on November 22, 2005 Ethicon is already aware of **"19% bladder perforation risk for TVT SECUR."** This type of risk information contradicts that the TVT-SECUR is "less invasive". A bladder perforation was recorded for Dr. Varma, an experienced gynecologist familiar with TVT and the U approach of the Design Validation Study using a cadaver, on Day 1 (9/21/2005). The risk was attributed by Ethicon's observers as failure to follow the IFU.

148. Ethicon's Clinical Expert Report GYNECARE TVT SECUR System signed by Dr. Martin Weisberg, Ethicon Senior Medical Director, Ethicon on December 2, 2005 indicated that the bladder perforation rate for the medical literature was 3.8%. The Ethicon data had bladder perforation rate for TVT as 0.002%. Therefore, it was significant that by November the risk for bladder perforation with TVT-SECUR was 19%.[67]

[67] ETH.MESH.03714002

d. Ethicon's 510(k) Clearance Did Not Relieve Ethicon from the Duty to Market a Safe and Effective TVT-SECUR System for SUI

149. On November 21, 2005 Dr. Herrera wrote his "Clinical Review" to Dr. Herbert Lerner. He indicated that he had reviewed the company's response to FDA's letter on October 4, 2005. On October 14, he had a discussion with members of GYNECARE, including Marty Weisberg, M.D., Dan Smith, Jennifer Paine and Patricia Hojnosky. They were able to clarify for his understanding the device and the Hammock and U approaches, providing additional explanation and new diagrams. He also received a description of the sheep study using the fingered device as well as the cadaver study. Dr. Herrera continued that Ethicon:

> *...has presented an additional predicate device, the Gyne Ideas Mini tape RP (K023898). GYNECARE presented in vitro-tissue simulation and animal model to demonstrate that the mean force in excess of 10N would be required to dislodge the Mini tape device.*[68]

150. As a result of the company's response and the testing of the newly identified predicate, Dr. Herrera now indicated that with the company's response to prior deficiencies he no longer had any urological clinical issues to preclude approving the submission. Dr. Herrera no longer suggested that Ethicon conducted a clinical trial with 12 month follow-up before 510(k) clearance. However, Dr. Herrera is making a regulatory opinion about clearance of 510(k) based on Ethicon's providing a cleared predicate. This is not to be confused with a scientific or medical opinion that the TVT-SECUR procedure will be safe and effective when used for SUI for patients, only that Ethicon has met the FDA's standard for 510(k) clearance.

151. Dr. Lerner then wrote his November 21, 2005 510(k) Memorandum to the record "Based on the sponsor's responses and Dr. Herrera's recommendation, I will SE the device."[69]

152. Ethicon was able to get its 510(k) cleared for TVT-SECUR but it required identification and comparative testing of the TVT-SECUR in terms of a new mini tape predicate device Gyne Ideas Mini tape for 510(k) clearance. Ethicon was also able to merely cite the history of TVT, TVT-O, Prolene, ETHISORB Dural Patch, Vicryl and PDS suture as components with a history of safe implantation in humans for the production of new TVT-SECUR SYTEM. Dr. Herrera in his clinical review of September 2005 had identified significant safety concerns for the TVT-SECUR not present with TVT or TVT-O Systems. Despite the clearance as SE to Gyne Ideas Mini tape, based on the internal documents clinical and lack of adequate disclosure to the FDA in the 510(k), those concerns, including ones seen in the Design Validation Study remained unresolved and not adequately addressed by actions of Ethicon.

153. There is an internal Ethicon email chain starting with Raimo Sump to Dharini Amin and others stating "Subject: TVT SECUR Minutes-Team meeting November 22nd 2005 _Agenda November 29th 2005. Note that the Ethicon CER for the TVT SECUR dated December 2,

[68] ETH.MESH.07876572
[69] ETH.MESH.07876572

2005 would list the bladder perforation rate in the urological medical literature as 3.8%, the internal documents for TVT as 0.002% and in the literature can be as high as 19% in patients with prior surgery. However, the TVT SECUR bladder perforation was 19% with one occurring with Dr. Varma in the first day of the Design Validation Study."[70]

> *Regulatory*
> *CE submission planned for last week of November;*
> *Pending on:*
> ○*Final Clinical Expert Report*
> § ***F/U Marty/Dan regarding 19% bladder perforation***
> ○*Design Validation Report Finalized*
> ○*dFMEA and aFMEA*
> ○*Both FMEA are in progress*
> *-According QA CE-submission can be done without Design Review about the Design Validation*
> ○*In this case the CE-submission will take place under risk to do it again, if the outcome from the Design Review is action items required.*
> *-No feedback yet from FDA regarding 510(k) submission.*[71]

154. On November 30, 2005, Patricia Hojnoski, Ethicon's contact with the FDA for the 510(k), wrote an email to members of Ethicon including Raimo Sump, Dharini Amine, Gary Borkes, and others:

> *Dear Team,*
>
> *GREAT news! Today we received 510(k) clearance for the GYNECARE TVT SECUR System. Congratulations to the entire team!*[72]

155. Barbara Schwartz, Ph.D. Worldwide Vice President Product Development "Fabulous news! Kudos to the team…"[73]

156. Quentin Manley to Barbara Schwartz, Patricia Hojnoski, Raimo Sump, Gary Borkes, and others, but no listing of Dan Smith despite his mention in the email, sent December 2, 2005. There is no mention of Ethicon ensuring product safety and efficacy when commercial use begins or collecting post market data now that Ethicon is not burdened with having to conduct a clinical study to obtain 510(k) clearance:

> *My thanks to Dan, the project team and all contributor. We should not forget that the FDA's initial response was to request a year of additional clinical data- so the value of your success is not just an on-time 510(k)- it is a considerable saving of resources, time and potentially delayed sales. Your handling of the*

[70] ETH.MESH.03714002
[71] ETH.MESH.05498580
[72] ETH.MESH.05498580
[73] ETH.MESH.05498580

situation was prompt, professional and well thought out- and here we have the result.[74]

e. As FDA Was Not Informed Ethicon's Design Validation "Before" 510(k) Clearance Identified Significant Issues with the Design and Placement of the Mini TVT-SECUR Sling

157. At the initial surgeon use of the TVT-SECUR, (Design Validation) before FDA's 510(k) clearance, with specially selected surgeons familiar with TVT procedures for SUI, Ethicon already had evidence of the risk of a surgeon pulling out the device while removing the inserter and trauma to the bladder.[75] Ethicon knew that the risk for sling removal by the inserter was greatest when implanting the 'U' shaped sling. However it did not notify the FDA and update its 510(k), it did not update the warnings for physicians in its IFU or marketing to warn about risks and difficulty with removal of the inserter and bladder injury. For evaluation of the product, Ethicon required a minimum of six surgeons to participate in the Design Validation Study. There was to be at least one surgeon that was a Gynecologist, as well as a Urogynecologist or Urologist. The surgeons were to all have been previously trained in sling procedures and have differing levels of experience with TVT products for SUI. Prior to participation in the Design Validation Study, each of the surgeons were to receive training on the components of the GYNECARE TVT-SECUR system.[76] Physicians were to evaluate the design of the package as well as the performance of the device and complete a questionnaire at the completion of product evaluation including evaluation of the performance characteristics. The primary criteria for success of the product was fulfilment of performance characteristics being assessed.[77] There were also Ethicon observers of the surgeons.

158. In Amendment 2 to GYNECARE's Design Validation Study dated October 18, 2005 (still before FDA's clearance) on Day 1 (9/22/05) there were already difficulties being identified by surgeons with the contents of the draft IFU. On Day one (9/22/05), a surgeon made the insertion/dissection through the patient's lower urinary tract during a "U" procedure. The surgeon stated that he might have made the initial incision incorrectly. Another surgeon on Day 1 did not use the Foley Catheter Guide, as he did not usually use one during a standard TVT procedure.

Based on Day 1 results, the procedural detail (IFU) was revised to change the use of the Foley Catheter Guide for the U –approach from an option to a requirement, and potentially reduce the likelihood of incorrectly advancing through the lower urinary tract.

159. On Day 1, another surgeon forgot to remove the protective cover from the 2nd inserter before he started to insert the inserter in the patient. Although surgeon "unmistakably stated", that the device design, IFU details and the video were clear, however, the team decided to highlight insertion information in the pictures from the big prints of the procedural step

[74] ETH.MESH.05498580
[75] ETH.MESH.05473737
[76] ETH.MESH.05530893
[77] ETH.MESH.05530893

guideline. On Day 2 (09/27/05), another surgeon successfully placed the implant on one side, able to remove the inserter from the first side. However, on the second side, he placed the device properly, but then he pulled out the device while pulling out the inserter. (The surgeon was not asked to repeat the procedure with a new device). The team members in attendance determined that the surgeon that dislodged the sling with removal of the inserter because he had not followed the IFU. (i.e. user error)

160. According to Ethicon's observers, that surgeon was supposed to pull the inserter out gently without forcing of the device and to reconfirm complete release of the device by pulling the release wire to its Stop-position, and determine if resistance was encountered. The other study participants on Day 1 and 2 had successfully been able to place the device without this occurrence with the inserter.

161. Based on the outcomes of Day 2, it was decided by Ethicon's observers to update instructions as explained above, and to conduct three additional 'evaluations.' This was permitted by the original study protocol requirements (a "minimum of 6 procedures"). These additional cases were to evaluate the TVT-SECUR device regarding the 3rd issue by completing three additional 'U'-procedures. The U-procedures appeared to represent the worst-case (most risk) for device pullouts to occur. So Ethicon knew before 510(k) clearance that the TVT-SECUR U procedures were technically more difficult to perform by surgeons with its mini sling SIS kit than 'H' procedures. However, Ethicon continued to request clearance to market the TVT as a Universal System able to implant both mini U and H shaped slings. Therefore, before 510(k) clearance Ethicon was already on notice about the risk for the inserter to pull out the sling and the increased difficulty implanting a TVT-SECUR U sling for SUI.

f. Ethicon Internally Knew the TVT-SECUR Was Unlike Any of the TVT Predicates

162. Unlike TVT and TVT-O, both with the tape mesh exiting from the woman's skin to help hold the mesh in place initially until tissue ingrowth, TVT-SECUR did not exit from the woman's skin (i.e. exit less). Unlike the predicates, TVT-SECUR implanted a smaller ('mini') Prolene tape sling without an exit as a single incision sling (SIS). Because there was only one single incision to place the sling, Ethicon called TVT-SECUR an 'exit less' approach with the implication to FDA's reviewer that Ethicon had determined that the exit less insertion was "less invasive" for a patient. The claim of less invasive was supported only by a change in the number of incisions. There was no supportive scientific data supplied to FDA by Ethicon to support a claim that the TVT-SECUR as SIS actually translated into clinically meaningful benefit of less invasion including less patient internal injury, less blood loss or improved outcome for treatment of SUI.

163. In November 11, 2004 Ethicon's Developmental Contract for TVTx discussed the SIS 'exit less' implant:

> *The objective of TVTx is to develop a less invasive 'exit less' device which will enable the physician to perform a suburethral sling procedure placing*

PROLENE mesh under the mid urethra without either the delivery device or the implant exiting the skin.[78]

164. For Ethicon's product claims for TVT-S marketing Ethicon knew it could obtain the claim "less invasive" from FDA for an SIS without providing FDA with any additional support:

Product claims will be similar to our classic TVT products, but will add additional claims of being less invasive which should not require a study to validate.[79]

g. Ethicon Called TVT-SECUR a Universal System Able to Implant "U" or "H" Approach Mini Slings

165. Ethicon, because either a U shaped or an H shaped sling could be implanted, chose to call the TVT-SECUR, its 'Universal System'. However, despite the claim as Universal, Ethicon did not have surgeons continue to use the same implantation procedures learned for TVT and TVT-O to implant its modified mini sling. FDA was told that the proposed TVT-S kit consisted of the Prolene tape with Ethisorb, two curved stainless steel single use introducers (inserters) that were fixed to the ends of the implant via a wire through the coated ends and inserters. There was not adequate discussion of the differences in risk and outcomes using the smaller TVT-SECUR sling, despite Ethicon's marketing plan to call it a new SIS 'mini' sling device.

166. The first Day of the first use of the TVT-SECUR in Ethicon's Design Validation Study for insertion of a 'U' shaped mini sling showed the difficulty of an experienced TVT user with removal of the new inserter and continued attachment with appropriate tension of the implanted sling. Ethicon added three more U sling insertions in the Validation Study to look at the difficulty with the inserter and tension. Despite Ethicon's marketing plans to promote the TVT-SECUR as universal system, there were differences in the technicality of completing the two procedures. One immediate option for Ethicon before commercial launch would have been to discontinue marketing efforts for placement of a U shaped mini sling and focus its research efforts on developing adequate instructions, methods and accessories and post-market clinical follow-up of the SIS 'H' sub-urethral mini hammock for SUI.

167. Instead of updating the FDA on the risk of the U sling or updating its warnings about the difficulty with inserter removal and sling positioning, Ethicon chose to continue to promote the TVT-SECUR as a Universal System and re-examine the inserter. In its December 10, 2005 Amendment based on the Design Validation Study it sought to satisfy that the inserter would not pose a "hazard for the patient or the surgeon."[80]

[78] ETH.MESH.01217673
[79] ETH.MESH.01217673
[80] ETH.MESH.04385380

h. Ethicon Failed to Adequately Study the Acceptability of Ethisorb Dura Patch When Proposed For Fixation of Its Next Generation TVT-SECUR 'Mini' Sling

168. Dan Smith in the TVT-NEXT (TVTx) Development Contract dated December 6, 2004:

> *The COGS are higher than current TVT products due to the addition of two layers of DURAPATCH (which consists of ETHISORB with a PDS film layer bonded on one side) to each end of the mesh.*[81]

169. For TVT-SECUR's 510(k) clearance, Ethicon opted to use 'Ethisorb Dura Patch' (an already cleared absorbable fleece material with absorbable material as a synthetic Dura Patch). Ethisorb was cleared by FDA in 2000 as various sized square sheets of 'Codman Ethisorb Dura Patch' (21 C.F.R. § 882.5910) which could be cut to the desired size by the surgeon. It was cleared by ODE's Neurology Devices Branch and intended as a bridging material for spanning deficits (gaps) in the patient's dura mater (brain's surface covering) (K991413). According to the 510(k)'s device description the Codman ETHISORB Dura Patch is composed of composite fleece fabric of polyglactin 910 and polydioxanone yarns, with a polydioxanone (PDS) film dyed violet on one surface. The porous structure of the fleece allows tissue on-growth. The PDS film coating on one side is to minimize leakage of cerebrospinal fluid (CSF) through the patch. Therefore, the PDS film is essentially to make the patch impermeable to fluid, a use not apparently needed for the proposed pelvic application. Animal and clinical trials were used to demonstrate that the DURA PATCH was suitable for its intended use as a dura patch for the brain. The implant material is fully biocompatible and absorbable over time.

170. The TVT-S Prolene mesh sling was to be sandwiched between pieces of fleece made of resorbable polyglactin 910/polydioxanone (Vicryl) coated with polydioxanone film (PDS film). When used as a dura patch, the Ethisorb Dura Patch is intended to be sutured in place at neurosurgery to help fill in the gaps in the dura and prevent loss of CSF. Eventually there would be tissue on growth on the fleece of the patch with re-sorption of the absorbable material. Codman and its technology (including the Ethisorb Dura Patch) were obtained by Johnson and Johnson following acquisition of Codman.

171. Before TVT-SECUR, Ethisorb DURA PATCH had never been cleared by FDA as an anchoring material or as an implant intended to be used as an active surface or placed without suture to initially hold it in place. However, Ethicon now proposed a totally new use for Ethisorb as part of the TVT-SECUR Systems and without any plans for additional anchoring of Ethisorb when implanted with the sling. To use Ethisorb, Ethicon as part of the Least Burdensome Method for obtaining FDA clearance, was able to merely reference the prior clearance of Ethisorb by 510(k) and successful commercial history as a permanent implant in the body. The FDA's reviewer of the TVT-S 510(k) was not informed there could be new and unaddressed issues of safety and effectiveness for this proposed indication for Ethisorb. If Ethicon had provided information about possible risks for Ethisorb in the TVT-S 510(k), this may have been sufficient to trigger a FDA reviewer to be able to request

[81] ETH.MESH.01217673-ETH.MESH.01217690

additional data from Ethicon about the proposed use of Ethisorb for TVT-S and the intended marketing.For example, one possible concern is that one surface of the ETHISORB DURA PATCH is coated with an absorbable film of PDS to prevent the passage of fluid, (for example prevent CSF from leaking from the brain through the patch).[82] Since the tissue ingrowth Prolene relies on the ability of cells to migrate through the mesh pores, it is not clear the potential effect of the PDS film on the fleece would have on the tissue 'on growth' of the fleece and tissue ingrowth of the Prolene mesh and the fixation strength of the sling. This risk to the success of tissue ingrowth does not appear to have been adequately studied by Ethicon.

172. The FDA's website for cleared 510(k)s has the Ethisorb 510(k) Summary of Safety and effectiveness. There is no reference to Ethisorb Dura Patch being used by Ethicon to help secure the TVT-SECUR sling in place in the pelvis. The tissue on growth for the DURAPATCH would be on the fleece surface not coated with a PDS film. FOR TVT-S the Prolene mesh is sandwiched between two layers of DURAPATCH, placing one surface on each side of the Prolene mesh with a PDS film surface waterproof and able to prevent the passage of fluid through the sling.[83] The effects of two layers of DURAPATCH to sandwich the Prolene mesh was not investigated by Ethicon to determine the changes in the Prolene mesh for both short and long-term fixation.

173. The sheep animal studies by Ethicon were not designed to address the potential holding or securing ability of commercial TVT-SECUR as a Prolene mini sling sandwiched between thermally applied PDS film when compared to the implantation and fixation of the TVT sling. Ethicon only implanted Prolene strips with Ethisorb but without application of a pulling or twisting force applied in a living animal to simulate motion and forces in the female pelvis.

174. The FDA's website for the K052401 the "510(k) Summary" of TVT-S, as written by Ethicon, indicated that the Ethisorb coated ends were added to the polypropylene tape to "facilitate passage (stiffens the ends) and the placement (tactile feel for the surgeon) of the mesh implant."(K052401). Ethicon did not request that FDA clear claims for "fixation" of the mini sling as a permanent implant in a woman. The Ethicon Summary of TVT-S:

> *The modified device has the same technological characteristics as the predicate device, the form, fit, function and method of operation are similar.*

175. Ethicon's Draft GYNECARE Value Proposition Report Project TVTx of November 9, 2004, "Product Description" includes that ETHISORB is composed of two well-known absorbable suture and mesh materials Vicryl and PDS.[84] The advantages of using ETHISORB in the system is "good tissue fixation" and to "provide strong market differentiation":

> *ETHISORB consists of Vicryl and PDS.*

[82] ETH.MESH.01217673
[83] ETH.MESH.01217673
[84] PDS Suture is Ethicon's absorbable suture of polyester polydioxanone and it is indicated for soft tissue approximation and ligation. Vicryl is also Ethicon's absorbable polyglactin 910 synthetic suture indicated for soft tissue approximation and ligation.

DURAPATCH consists of ETHISORB and a PDS film layer.

...ETHISORB provides stiffness to the mesh which results in good fixation strength in the tissue. ETHISORB will be unique to TVTx and will provide strong market differentiation. ETHISORB is absorbed in approx. 30-60 days...[85]

176. Internally in the Development Contract of November 30, 2004, Ethicon discussed the benefit of Ethisorb Dura Patch for sling fixation:

ETHISORB & PDS film provides stiffness to the mesh to allow implantation and has a good tactile feel, initial fixation is achieved is equal or greater than our current TVT which exits the abdomen. This has been proven in the pre-clinical animal study.[86]

177. GYNECARE's Description of the Competitive Advantage of TVTx included that the Animal/Sheep data support tissue ingrowth at 1, 2, 4 & 12 weeks. Histology report from animal/Sheep data support similar absorption rates as base line ETHISORB studies. Ethicon's final statement about the advantages of Ethisorb was that it left behind no stiff material or anchors:

Uniqueness of ETHISORB and no permanent stiff material or anchors.[87]

i. Ethicon's Tradename "*TVT-SECUR*" Falsely Implied Improved Mini Sling Holding and Unsupported SUI Benefits

178. Ethicon's marketing knew that the new trade name for Ethicon's mini sling would be "TVT-SECUR". The name and the additional product features, all served to falsely imply to surgeons that, unlike Ethicon's TVT and TVT-O Systems, called tension free vaginal tape systems, that Ethicon's newest modification for its SIS mini sling called TVT-SECUR System, (implanting a mini Prolene tape without needles and with added Ethisorb Dura Patch), somehow had demonstrated by Ethicon a potential to provide a clinical improvement in the treatment of SUI. The 510(k) for legally marketing the TVT-SECUR in the United States was cleared by FDA on November 28, 2005.

179. However, before April 2005 the new 'mini type' SIS TVT product had only been referred internally as 'Next Generation TVTx.' In an April 25, 2005 email sent widely throughout Ethicon by Raimo Sump, Engineer, Procedural Implants R&D, with an agenda for a Design Review Strategies Meeting was attached an email Subject: TVT SECUR Minutes- April 19, 2005 Strategy Review. The plan for first human use of the parts was for September 1. 2005 with a launch of 1500 products on January 2006. Internally there was to be a document showing that TVT U (TVT Universal) was the same as TVT SECUR:

The new project name as well as product name is TVT SECUR. Last week the Board decided to accelerate the full launch.

[85] ETH.MESH.06705963
[86] ETH.MESH.01217673
[87] ETH.MESH.01217673

Launch date per charter document: 09/06;

FHUP per charter 09/01/05 (September 1st 05); First Human Use (Parts) will be executed by Walther Artibani and Mickey Karram

Initial launch product: 1500 Products available for January 06....

An overall document will be written that explain TVTU and TVT SECUR are the same. [88]

180. Both American physicians and FDA would not anticipate that Ethicon, the acknowledged expert marketing the 'gold standard' of TVM mesh for SUI, would consider marketing a new TVT product for SUI without having conducted adequate testing and development or that Ethicon would knowingly sell a potentially less safe product for SUI rather than its prior TVT products. The use of the TVT-SECUR product name falsely implied to surgeons Ethicon's system offered as an improvement, a more secure sling, for SUI when compared to Ethicon's earlier products.

181. Ethicon's 510(k) did not request that FDA consider a comparative claim that the Prolene mesh tape with Ethisorb was 'secured' or held in place better until tissue ingrowth than TVT or TVT-O tapes. Instead, Ethicon only requested that FDA clear the SIS TVT-SECUR System as 'substantially equivalent' to TVT and TVT-O. This is further supported by the published 510(k) Summary of Safety and Effectiveness for TVT-S on FDA's website. The Ethicon published document states that Ethisorb was added to the ends of the mesh sling to help the surgeon move the tape (stiffen the ends) and to assist in sling placement (improved tactile feel for the surgeon).

j. Ethicon Significantly Changed TVT-S Implantation Technique and Knew Its New Inserter Was Difficult for Surgeons to Use Successfully 'Before' 510(k) Clearance

182. Despite Ethicon's 510(k) claims to the FDA review of substantial equivalence to TVT and TVT-O and no new issues of safety and effectiveness, the SIS TVT-S inserters (introducers)[89] had never been used commercially in patients with either TVT or TVT-O and were still sharp and able to cut tissues as had been the insertion needles for the prior devices. For TVT-S, Ethicon had used a new mini length of laser-cut polypropylene tape than either of the predicates and the mechanism of insertion (single incision) would be markedly changed from the predicates.

183. Other than in Ethicon's 510(k) submitted to FDA, there were striking differences in the TVT-S compared to the predicates. A KOL for Ethicon even commented to an Ethicon employee on November 2007 that "TVT-S is so 'utterly different to the other TVTs that it probably shouldn't be called a TVT' and the speed to market and breadth of launch did not

[88] ETH.MESH.06274935
[89] Dr. David Robinson deposition 7/24/13 p. 116, L5-22

take this into account."[90] Ethicon's World Wide Medical director in 2007, Dr. David Robinson, recognized that the TVT-S was "a sling 'unto itself' as far as techniques go."[91]

184. About the introduction of laser cutting of the mesh tape, the Development Contract of November 11, 2004 had that the introduction of laser cutting was based on physician perception and not internal testing by Ethicon as to the effect of the thermal changes produced on the shorter mesh sling edges:

> *The same PROLENE mesh will be utilized as per exiting TVT and TVT-O device, however, it may be cut via laser to improve the handling characteristics as expressed by many surgeons who use competitive tapes. Due to the ease of placement and short placement pathway, the plastic sheath will not be required for the tape adjustability.*[92]

185. Despite Ethicon referring to the TVT-S as "less invasive" based on the use of a single incision, the 510(k) did not adequately inform the reviewer that this 'benefit' did not meaningfully translate into the TVT-S insertion being easier for a surgeon to learn and perform than the prior multiple incision predicate TVT and TVT-O procedures. The new single insertion sling (SIS) of TVT-S was known by Ethicon to be difficult. The removal of the sling inserter would dislodge anchoring of the TVT-S tape. The TVT-S tape was difficult to tension properly due to the surgeon's mechanical difficulties holding on to the patient's tissues while attempting to remove the inserter and trying not to dislodge the tape. These technical and design difficulties with TVT-S added to problems for a surgeon keeping the mesh under sufficient tension and in place. These difficulties were not present with the TVT or TVT-O Systems. Ethicon was aware that because of the risks despite a SIS the TVT-S was at greater risk of failure for a patient than either TVT or TVT-O. the TVT-S would fail to be able to maintain the angle of correction at the urethra to help control SUI, resulting in greater risk for inadequate fixation and lack of development of adequate support within the first 12 weeks post-operatively to correct SUI. These tensioning and fixation problems for TVT-S and risk for failure were significant and well known to Ethicon[93] but were not well described to FDA in the 510(k) or to physicians in the product marketing information and instructions.

186. Aside from TVT-S tensioning and difficulties placing the TVT-S by a single incision (SIS), Ethicon's decision to use Ethisorb without obtaining additional pre-clinical or clinical information to support its ability for temporary anchoring of a sling sub-urethral in the female pelvic floor, its choice could have helped contribute to the increased risk for failure of TVT-S.

187. Another foreseeable risk for TVT-S based on the prior history of tissue ingrowth in Prolene mesh for TVT and TVT-O was the difficulty to remove a transvaginally placed mesh when and if complications occurred. Despite the known increased risk for corrective surgeries for

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[90] ETHM.MESH.00327062
[91] ETH.MESH.006442328
[92] ETH.MESH.01217673
[93] ETH.MESH.00329316, ETH.MESH.05473738, ETH.MESH.05530459, ETH.MESH.05530464, ETH.MESH.05530469

TVM mesh complications with TVT-S, including potential damage to nerves, bladder, further scarring and retraction, Ethicon's IFU and training provided surgeons for TVT-S provided no established treatment guidelines for as to how to deal with complications and treat patients. Ethicon knew of these increased difficulties and risks based on its other TVT products as well as the added morbidity. However, with TVT-S Ethicon was aware that there was an increased risk for failure and need for surgical removal of TVT-S but still failed to adequately warn. Ethicon proposed TVT-S as a permanently implanted TVM SIS with no voluntary updating of its recommendations and warnings in the IFU or physician training.

188. In its initial Device Validation Study (**September 21-22, 2005**), as discussed above, Ethicon's group of TVT experienced surgeons trained on the TVT-SECUR components had difficulty with a stationary cadaver, (not a living and moving patient) removing the new inserter without displacing a 'U' mini sling. Another surgeon (Dr. Varma)[94] placed the 'inserter/dissection' through the lower urinary tract (i.e. perforated the bladder) of the cadaver.[95] Ethicon after 510(k) clearance on December 2005 wrote about this issue in its December 2005 Design Validation Report for Dr. Varma (U-approach):

> *...the IFU clearly states that each inserter should be advanced in two steps to avoid this problem. During the insertion of the TVT SECUR, Dr. Varma did not use the catheter guide.*
>
> *– See Corrective Action 1 (45^{0}hand angle for U-approach)*
>
> ***-See details in Corrective Action II (Use of Foley Catheter Guide for the U-approach)***[96]
>
> *Question C Did the specimen possess any anatomic abnormalities or previous sub-urethral sling surgery?*
>
> *○Yes: The specimen did have a grade 2 rectocele as well as a grade 2 vault prolapse*
>
> *○The specimen did not have a uterus*
>
> *Question 1: Do you routinely do both Hammock & U*
>
> *○No: Primarily Standard TVT (U-approach)*
>
> *Further surgeon comments:*
>
> *○Following the placement of the first side, the second side does not have enough room to maneuver (space is tight). The first side is easier to place than the second side, but still, placing the second side is "doable".*

[94] ETH.MESH.05530449
[95] ETH.MESH.05473737 (Amendment 2 Design Validation Study- October 2005)
[96] ETH.MESH.05530449

189. Dr. Daniele Grassi (H- approach) inserted the second inserter without removing the inserter protective cover. His usual procedure is a Trans-obturator approach. "Once it was clear that the surgeon had missed an important step the project leader decided to interrupt the procedure and reminded Dr. Grassi to remove the protective cover. "He then did so, saying he was nervous and the protective cover could not be more obvious."[97]

> ***See details in Corrective Action III (Remove the protective cover was added in additional places and bolded.)***[98]
>
> ***Further surgeon comments:***
>
> *Following the placement, the surgeon commented that he felt the tape was looser than he preferred. Further elaborated that this could simply be a learning-curve issue with a new device.*
>
> ***See details in Corrective Action Section***
>
> *Some resistance was noted during removal of the second inserter*
>
> ***See details in Remarks of Corrective Action Section***
>
> ○*TVT-S will require a different approach to tensioning the implant as compared to regular TVT or TVT-O. This is due to the fact that you do not need to remove any sheath nor allow any slack for tightening the implant as the sheath is removed. Learning curve for this procedure should be short for those who currently use the TVT product.*
>
> ○*The cadaver/specimen was tougher than live tissue...*
>
> *Some resistance was noted during removal of the second inserter.*[99]

190. Additional Design Validation evaluation was performed on September 27, 2005 with cadavers as Part 2: IFU Version V5A, Big Prints…Amendment 1. Dr. Cheryl Iglesia used the U approach, an approach she preferred clinically. She performed the procedure as explained and trained without issues. Following the insertion and check of the position, the first release wire needed to be pulled to its "STOP" position. She pulled the first release wire "very hard" and in doing so she pulled the release wire completely out of the device. Dr. Iglesia pulled out the fleece/implant with the inserter:

> ***See details in Corrective Action IV (Pull of the release wire to its Stop-Position was emphasized)***
>
> *The removal of the first inserter happened without issue, although it was not pulled out gently as specified in the IFU*

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[97] ETH.MESH.00997626-ETH.MESH.00997642.
[98] ETH.MESH.05530449
[99] ETH.MESH.05530449

The second inserter release wire was not pulled completely to its "Stop"-position and the removal of the second inserter was again not done gently. During her removal of the 2nd inserter, Dr. Iglesia forcefully pulled out the implant on the patient's left side.

See details in Corrective Action V (Correct pull out of inserters)

Further surgeon comments:

Wire completely disconnected during removal on the Patient's right side

Wire not completely disengaged prior to applicator removal-fleece/implant was pulled out with the inserter

Possibly safer than base TVT or TVTO.[100]

191. Amendment 2 Part 3 was Design Validation testing on October 19 and 21, 2005. There was evaluation by three surgeons, with all 3 implanting a system by a U approach. The surgeons were Dr. Scott Smilen, Dr. Shyam Hataganadi, and Dr. Mark Mokrickye.

As Dr. Smilen pulled out the Release Wire on the second side, the wire did not stop at its "Stop" position

Corrective Action IV (Pull out the release wire to Stop-position[101]

192. For Dr. Mark Mokricke, the comments:

Suggested IFU and picture change: Step &: "inside straight groove"...

A little confusing about how to grab the wire and the inserter[102]

193. There are a series of internal emails in October 2005 regarding the IFU as well as Design Validation for TVT-SECUR and clinical comments regarding changes for the IFU.[103] The first is an internal October 24, 2005 email from Gary Borkes, Design Quality Engineer, Worldwide Quality Engineering, Ethicon to Dan Smith, Raimo Sump, Martin Weisberg, Naomi Sinclair et al (R&D) "Subject: TVT S Des Val Comments":

Please note-these are thoughts or comments that were shared from Dr. McG-they are not Des Val outcomes of deficiencies in meeting user needs...

He commented that (somehow) he was shown how to attach the needle holder prior to starting the training; and if it wasn't for that, in his opinion the technique was not clearly defined via the draft IFU verbiage or the picture. He

[100] ETH.MESH.05530449
[101] ETH.MESH.05530449
[102] ETH.MESH.05530449
[103] ETH.MESH.00526111

felt there might be some benefit to showing it more clearly in the Procedure Steps pictures.

[Smith, Dan [ETHUS]] -There WILL be a video and it WILL show the device being connected, disconnected and everything in between. The verbiage is correct as written and would be incorrect if written as Dr. Mc has suggested. There is NO need for another picture and I am not going to ask that one be created.[104]

194. On October 24, 2005 Dan Smith sent a response email to Gary Borkes, Raimo Sump, *et al.*, "Subject RE: TVT S Des Val Comments Importance High." Mr. Smith, an engineer, clearly responded that he would not consider any additional comments from a surgeon, which had performed an evaluation of the TVT-SECUR as to what was needed for a clinician to implant TVT-SECUR in the IFU. He called such comments a "waste of time".

Gary please find my comment below and do not take it the wrong way, but I am through making non value add changes to a document that is 1000 times more accurate and complete than TVT.

I have drawn the line, unless someone can demonstrate a "real" deficiency in the document. This is a waste of time and it is holding up the project in many ways.[105]

195. Gary Borkes sent an internal response email on October 25, 2005 back to Dan Smith, Raimo Sump, and others, "Subject RE: TVT S Des Val Comments" makes it clear that there are time constraints to get the TVT-SECUR project completed, that Dan Smith is heading the project efforts, that the TVT IFU is dated and the TVT-SECUR still requires adequate Design Validation efforts from Ethicon. At this time the FDA has still not cleared the 510(k). In the Ethicon Design Validation Report, Table 2 of December 10, 2005 there is no surgeon with the name McGricky. [There is listed a female "inexperienced Uro-gynecologist" by the name Heather McGehean that implanted two TVT-SECUR by U approach, the first on September 27, 2005 as a "pass" and the second listed as a ½ hour procedure "performed directly after the official Des Val date- and not included"[106]] However, Mr. Borkes refers to a "he" so it is not clear that the information is present in the Design Validation Report Table 2:

Thanks for your explanations below. I'm not quite sure what I would take the wrong way??

Please don't take this the wrong way....but why do you think we are doing Design Validation exercises? It is not just another hurdle to "pass," although I get the impression that some might feel that way. The reason we take the device to users in Design Validation is to illicit their input, not to help or coach then to pass attest. It is to confirm the product meets their needs, including packaging

[104] ETH.MESH.00526111
[105] ETH.MESH.00526111
[106] ETH.MESH.05530471

> *and labeling. It is the responsibility of the "team" to evaluate the input and determine what is a true "need" , what revs are required, what is preference, what is wish list, and what is opinion. Although you are absolutely a great product expert, I believe the team extends beyond you. If our MA and Clinical team members were not in attendance, then it is more than appropriate to make sure that they hear the input and evaluate whether or not it holds any clinical significance or can improve the use of the device for the user base. I believe the timeline pressures are recognized and felt by everyone- believe me Dan everyone I talk to says how under the gun they are and how much they are trying to push to support you and the project despite the overwhelming load ...But we also have to properly evaluate user input, or it could bite the product dose the road. McGricky (sp?) seemed like a logical and knowledgeable user...*
>
> *As far as TVT base- the bar should properly not be "as good as". It is a rather mature product purchased from elsewhere and the requirements for design control, risk assessment, and other things that feed into the IFU have changed since then. This current device needs to be able to meet its unique needs.*[107]

196. Despite the internal knowledge that the TVT-SECUR was a system different to implant than TVT, in Ethicon's internal December 10, 2005 Final Design Validation Report, Ethicon indicated that it felt 6 surgeons were sufficient to evaluate the 'U' and hammock in cadavers because of the "*extensive market experience of the TVT mesh.*" Ethicon continued that based on the experience with cadavers as well as Ethicon's own staff with cadavers the TVT-SECUR design was adequate:

> *Additionally, numerous cadaver labs were conducted both with surgeons, marketing, R&D and Medical Affairs personnel to design and develop the TVT SECUR device, package and labeling. All this information is either in the Clinical Expert Report (CER) or the Design Dossier documents.*[108]

197. The project leader for the "Procedures for Evaluation of the Product" was Engineer Dan Smith, the individual responsible at Ethicon for the design and testing of the final TVT-SECUR system. All product evaluations occurred at St. Peters University Hospital, Minimally Invasive Learning Center, New Brunswick, NJ for all Design Validation Testing (9/2005). A total of 13 surgeons participated in the evaluations.

198. The Design Validation Study Report was dated December 2005 and included Ethicon's protocol for additional surgeon cadaver evaluation as "Part 4" Amendment 3 (also dated December 10, 2005). Ethicon's Design Validation Report and the Amendment 3 (Part 4) to the Design Validation Study were both dated December 10, 2005, less than one month after FDA's 510(k) clearance. Amendment 3 (Part 4) provided additional discussion as to why surgeons were not provided the actual components intended for commercial use in living patients for TVT-SECUR in the United States when evaluating the performance of the product with cadavers. Reportedly, the purpose of the Amendment 3 (Part 4) was to provide "objective evidence" that the final GYNECARE TVT-SECUR System satisfied the user

[107] ETH.MESH.00526111
[108] ETH.MESH.05530449 (Product Design Validation Report December 10, 2005)

need of "the release wire should not spring back after being pulled out to its Stop-position" in normal use and is not a hazard for the patient or surgeon." Issues to be re-validated included according to Table YY: "bladder perforation, removal of protective cover, implant pull out and wire pull out."[109]

199. According to the Report's Table YY, for the Part 1 testing 1 bladder perforation occurred and confirmed 9/27/05 with a total of 6 'U' slings performed and not seen for H slings placed; "Removal of protective cover" issue confirmed October 21, 2005, 6 U procedures and 6 H slings required but not applicable to H; "implant pull-out" issue identified October 21, 2005 3 'U' procedures and not applicable to H procedures. The 'wire pull out' issues was confirmed by PQ and intended to be re-verified by Amendment 3 Part 4- 3 U procedures and 3 H procedures.[110]

200. Before conducting additional Design Validation Study protocol (Amendment 3, Part 4) the "targeted" implanting surgeons for participation (Gynecologists or Urogynecologists or Urologist) were each to have been trained by Ethicon on the GYNECARE TVT-SECUR System and components, including reviewing two videos (filmed 9/21) about implanting the 'U' and 'hammock' slings, a "Big Print" Procedure Steps Guide Line, the IFU, an exemplary of the PQ product (with/without open package) labeled "not for human use", Non-PQ Product (TVTS1 foil package and box) with final label to allow questions regarding the label[111]. The 3 participating surgeons at the end of evaluation were to complete a questionnaire:

> *The use of pre-production assembly fixtures was determined to be the root cause of the release wire pullout issue. Use of this assembly equipment resulted in variability of the location of the finger pad/wire/inserter relationship, which controls the release wire movement. The corrective action was to develop and redesign the assembly equipment, which was used for the Production Qualification (PQ) product.*
>
> *To validate the GYNECARE TVT SECUR SYSTEM regarding the above-mentioned user need, a minimum of six (6) complete procedures, three (3) H-approaches and three (3) U-approaches each, the target will be to use 3 surgeons if possible. The procedures will be performed in conformity to the intended use, within actual or simulated use environments in a manner consistent with the Instructions for Use (IFU) for GYNECARE TVT SECUR SYSTEM and surgeons' usual techniques. This will be accomplished utilizing a human cadaver model. The use of one surgeon would be sufficient to evaluate that the product will satisfy the above-mentioned user need, however we intend to use 3 surgeons. This will not only verify the corrective action on the wire was appropriate but also re-confirm all previous study "Parts" using PQ product.is product.*[112]

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[109] ETH.MESH.05530449
[110] ETH.MESH.05530449
[111] ETH.MESH.04385380 (Amendment 3 to the Design Validation Study- December 10, 2005)
[112] ETH.MESH.04385380

201. As written on December 10, 2005 by Ethicon, for Amendment 3, Part 4, since the testing was considered only to correct an "assembly issue", multiple surgeons were not required for evaluation, but 3 were used. A total of 6 placements were completed, 3 by the 'U' approach and 3 by the 'hammock' approach. No changes were made to the IFU or training materials. The only difference for the testing was that the device used. Ethicon concluded that based on the cadaver testing "confirms the wire pullout issue has been successfully resolved and no further testing is required." Ethicon's Table ZZ however showed the device of Part 4 was conducted "December 13 & December 14" (technically after the date of the December 10, 2005 Design Validation Report).

202. Ethicon's December 2005 Design Validation Report "DISCUSSION OF OBSERVATIONS AND TAKEN CORRECTIVE ACTIONS, Part VI REMARKS" indicates that the TVT-SECUR design is acceptable. There is no additional clinical testing support provided or plans for testing in living patients at the conclusion of the Design Validation Report. Essentially TVT-SECUR design is perfect and all issues are due to user error. However, these users are surgeons like Dr. Varma and Dr. Iglesias experienced with TVT sling insertion and have clinical experience for SUI not shared by Ethicon's engineers and marketing staff. Instead of a meaningful discussion of investigation of human factors necessary for inserting TVT-SECUR there is a discussion of "mathematically and correct insertion", that the design addresses the "tight space sufficiently" for both inserters and that "patient's tissue is flexible" and "fleece ends can bend upwards to give more length."

203. Based on this minimal product testing, with justification the history of TVT products, Ethicon concluded that additional changes were not required for the TVT-SECUR System on December 2005 based only on cadaver testing by 10 surgeons (not 13). There was no discussion that problems were experienced with the 'U' approach and included not only Dr. Varma (Experienced Gynecologist) but also Dr. Cheryl Iglesia (Experienced Uro-Gynecologist) and Dr. Scott Smilen (Experienced Gynecologist). Ethicon's Design Validation Report did not include evaluation and outcome of Dr. Jim Raders (9/27/05) (Experienced Uro-Gynecologist) second ½ hour procedure or Dr. Heather McGehean's (Inexperienced Uro-gynecologist) second "½ hour procedure" were not included in the final report. There was no discussion why difficulties were reported for only the U approach in the cadaver evaluations and not the 'H' approach.

204. Ethicon's Design Validation Report –"**Table 2 General information and Subjective Demographics":** Part 1 (9/2005) -4 procedures with 2 failures (50%) and 2 pass; Part 2 (9/27/05) -5 procedures with 1 failure (20%), 2 not included (40%), and 2 pass (40%) (or 3 procedures- 1 failure (33%) and 2 pass) ; Part 3 (10/19-21/05) – 3 procedures with experienced surgeons- 1 gynecologist and 2 uro-gynecologist and 3 pass but with a "pass with + Wire issue" (33%). So the failure rate for the 10 procedures accounted for in the Table 2, there were potentially 4 failures (including the "wire issue") for a 40% failure rate in terms of the adequacy of the design of TVT-SECUR when used in cadavers by experienced surgeons and all for the U approach. Yet, Ethicon's staff maintains the system as designed has been shown to be acceptable and no additional testing is required.

Dr. Varma mentioned, that the second side does not have enough room to maneuver (space is too tight)...His comment was clearly expected since he was observed as not following the IFU....The device design and procedural approach addresses the "tight space" sufficiently. The length of the mesh/implant stays in relation with the length of the inserters' tip, the fleece material length, as well as several assembling details. The interconnection of all of them allows mathematically and by correct the insertion of both inserters. Additionally the mesh is flexible, the patient's tissue is flexible, the implant fleece ends can bend upwards to spend even more length.

The root causes of the looser mesh position after pulling out the inserters is that, compared to standard TVT, no plastic sheet has to be pulled in the direction of tensioning the mesh. Moreover inserters stay close together and by checking the mesh position, they are pressed to the sides and by doing this they're tensioning the mesh; Both causes were addressed properly already in the IFU v3 ...It is clearly stated, that the final mesh position needs to be checked and if necessary further adjustment has to be done before removing the second inserter.[113]

205. There are a series of internal emails at Ethicon in December 20, 2005 after the Design Validation Report. The first is sent by Mark Yale, Director, WW Risk Management to Raimo Sump, Dan Smith, Patricia Hojnoski, Jeffry Everett, "Subject TVT SECUR design validation study" Importance: High (underlining for emphasis):

As I step into the role of leadership of the DQE function, I have been reviewing ongoing projects. In light of this review, I have concerns with the recent TVT SECUR design validation studies. Based on these concerns, I think the only path forward is to repeat the final study...I have a solid and defendable rationale for this decision.

TVT is one of the FDA focus devices. The September 2005 FDA was directed to TVT and MDR reportable events...It is fully expected that as some point in the future, the TVT SECUR project will be reviewed by the FDA in detail and we will need to defend the clarity of our documentation and defend that we followed procedures in its execution. Additionally as you all may know we have ongoing issues with PROCEED mesh in the field. These issue have raised organizational awareness that we may not have correct balance between our need for speed to market and getting this done right before we release. These two issues temper my opinions and decision in regards to TVT SECUR. Here are my concerns as I known them...

**Design validation protocol has had three amendments written to it. This have come due to issues with each execution and amendments were done to correct. Upon audit this approach unfortunately look like test till you get it right and is almost never cleanly defendable...*

[113] ETH.MESH.04385380

**For the third amendment, the study was executed prior to all signatures being on the study protocol and without the product having gone through PR563 release. Both of these are noncompliance with our procedures. Speed is never defendable excuse upon audit for noncompliance.*

To assure that my position is valid, I have discussed this with Cindy Crosby and from a compliance position she is an absolute agreement that we need to conduct a new study to correct these issues.[114]

206. The December 20, 2005 email from Allison London Brown sent to Quentin Manley with copy to Dan Smith and Bob Roda:

Again this response, while it may be valid, seems to be about a document and not if the device works of the validation was valid. My other issue is that we were following counsel from QA on each of the amendments. And to my knowledge you are very lucky to have a completely flawless dv.[115]

207. Bob Roda, Group marketing Director, WW, Urology, Pelvic Floor and Incontinence sent an email to Allison London brown and Quentin Manley with copy to Dan Smith, with a plan to have a meeting with Mark Yale:

Team,

....Mark needs to provide other viable solutions at this time.[116]

208. December 20, 2005 email from Quentin Manley to Bob Roda with cc to Dan Smith (underlining for emphasis):

...The reason is that QA already assume that the reason we are getting into this is too much urgency and that the prime motivator will be marketing.

...However, marketing urgency is one factor that might actually dissuade QA from making a favourable decision...[117]

209. Still on December 20, 2005 Quentin Manley sent another email to Bob Roba with copy to Dan Smith (underlining for emphasis):

OK. But let me warn you: argument "But we'll miss the launch deadline and we worked really hard," will only provoke a negative response...[118]

210. There is a follow-up email from Dan Smith to Quentin Manley and Bob Roda, with Dan Smith disagreeing there were any issues with his Design Validation protocol for TVT-SECUR as suggested by Mark Yale (underlining for emphasis).

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[114] ETH.MESH.06860393
[115] ETH.MESH.06860393
[116] ETH.MESH.06860393
[117] ETH.MESH.06860393
[118] ETH.MESH.06860393

Folks, if we are to come out of this at all, we must stick to the requirements (both DC and FDA) not interpretations but written words.

Let the chips fall where they may and then we can have the discussion as to what needs to be done and the impact of those actions.

Upon by detailed review or PR563-002 and PR800-011 there are NO compliance issues with regard to the following:

-use of Amendments in a design validation is not discussed (nor does the FDA say they can't be used). The FDA requires full disclosure of all pertinent information and data. The Amendments clearly do that and are a road map to where we are today and should not go away or be hidden.

-the way DV was conducted was in compliance with our procedures.

- there is no requirement to have an approved validation "protocol" only the final report which is under discussion.

-both our and FDA documents state that a Design Validation is to ensure that "devices conform to defined user needs and intended uses" it is NOT judging other company procedures unless they have or could impact the user needs and intended uses."[119]

211. Quentin Manley, Director of Product Development, Tissue Reinforcement Platform responded by email to Dan Smith: "Excellent work" Dan Smith's email to Quentin Manley (underlining added for emphasis):

> *...It will never work if QA is allowed to interpret the intent different than the written requirements.*[120]

212. There is a December 21, 2005 email from Quentin Manley to Mark Yale, David Robinson, Bob Roda, Allison London Brown, Dan Smith et al "Subject : Minutes of meeting TVT SECUR design validation discussion 20th Dec 2005. The purpose of the meeting was to discuss the ramifications of the recent TVT SECUR validation. Despite Mr. Smith's opinions the Design Validation was obtained in accordance with internal design control procedures, in contrast to the opinion of Mark Yale, the testing was to be redone. It was agreed:

> *The data generated from the recent TVT SECUR validation, although felt to be of good quality, might not comfortably endure the rigor of an FDA audit even though it has been generated in accordance with internal design control procedures.*[121]

[119] ETH.MESH.06860393
[120] ETH.MESH.06860393
[121] ETH.MESH.06860404

213. New QA cover to work on the team to close out the current validation protocol. The work was to "urgently" outline a new strategy with timelines and recommendations for the next validation steps. The current study with "acceptable results" was to be closed out. It was suggested that new language be used that that stated:

> *Although the product meets the user needs and intended use "for business reasons a new study will be repeated using potentially the "original" requirements.*[122]

214. A question was asked if there should be a possibility of conducting human clinical studies. The new Validation Protocol, despite Dan Smith's opinions that it had been performed correctly the first time, was targeted for January 9th and 10th, 2006.

> *PH and new QA person to look at the possibility of undertaking human clinical studies currently scheduled using PR 563-001 before validation close out. ...*
>
> *POD, R&D, and Marketing will start to arrange cadavers and surgeons for early January. This means we need to close out the old Validation, create a new Validation Protocol, have a design review, and approve the new study. Note: The target for this would be no later than January 6th, so studies can commence on January 9th & 10th.*[123]

215. After 510(k) clearance in 2005, Ethicon began a limited release of TVT-SECUR in 2006 to collect patient data. A January 22, 2007 email reflects that Ethicon had received 49 TVT-SECUR complaints from Germany including bleeding and hematomas but "most state 'failure incontinence after several weeks'" with Ethicon aware of these reports of premature failure in December 2006.[124] An internal email from Ethicon's Mark Yale indicated that TVT-S engineer Dan Smith travelled to Germany during the week of January 8, 2007 to meet with a surgeon experiencing problems with TVT-S. While there, Mr. Smith learned that other surgeons were having similar problems with TVT-S. A subsequent email from Mark Yale dated March 1, 2007 revealed that Ethicon knew of 50+ cases of treatment failure for TVT-S with some requiring additional intervention. Dan Smith, the designer of TVT-S, made multiple visits to Germany to "retrain preceptors and others." To address reports of premature failure with TVT-S, Mark Yale met with Ethicon's Medical Director David Robinson along with Dan Smith. The reason was to discuss erosion issues as a cause of treatment failures due to "what may be less than perfect surgeon training."[125]

216. In a February 9, 2006 email from Mark Yale to Gary Borkes and E Jacobs, Subject: Fw: TVT S DESIGN REVIEW (Design Validation):

> *Can you give me insight into where Raimo and Dan are at. For last two days at the leadership meeting I had everyone from Renee Selmen on down pulling me "aside" asking how the proverbial "we" get this project done. There is*

[122] ETH.MESH.06860404
[123] ETH.MESH.06860404
[124] ETH.MESH.0324086
[125] ETH.MESH.00330141

immense political pressure here and I need to actively manage the overall QE response,

Bottom-line if there is big steaming pile here (as I suspect), I need to know ASAP and push back hard on whomever to fix.[126]

217. Gary Borkes sent a reply email to Mark Yale and E Jacobs:

Mark-yes... there is a great deal of spin happening at this point, unfortunately

...The recent answer seems to be QA is holding up the works. This is far from the truth. But I have been advised to stay clear of the fray and not get caught up in the spin...

I believe there are significant issues that are open and need to be addressed out of the Matrix, but these are being glossed over with the report smokescreen...[127]

218. An internal email chain beginning with one sent from Raimo Sump to Raimo Sump , Dan Smith, et al dated February 3, 2006 Subject Design Review TVT SECUR (DRM and Design Validation Packaging):

TVTS is moving on, we will have to hold another Design Review. This is not yet the official invitation/agenda for that Design Review...The goal of the Review will be to approve the DRM inclusive the Design Verification column as well as to approve the Design Validation Report Packaging.[128]

219. Linwood Staub to Ed Jacobs Subject FW: Major Request for Help to get RE: Design Review TVT SECUR (DRM and Design Validation Packaging):

I understand there has been some issues here in the past but just wanted you to know that this is a huge hurdle for us in order to get A plus in the field. It is critical to our number and more critical from a strategic point of view with our customers...[129]

220. Ed Jacob responded to Linwood Staub and copy a sent to Mark Yale on February 10, 2006 (underlining added for emphasis):

Blame for delays is certainly being directed at QA and I am one of the ones who as an independent observer has identified practices that did not conform with the Design Control procedures and process....the FDA was in the facility in September on the TVT family. The auditor stated that he would recommend an audit of the Neuchatel facility as relates to the TVT family of products. We want to make sure that this project, being the new product in the TVT family, can

[126] ETH.MESH.00326236
[127] ETH.MESH.00326211
[128] ETH.MESH.00322464
[129] ETH.MESH.00322464

> *withstand the audit and not result in situation where our work on TVT-S negatively impacts our ability to distribute the TVT family.*
>
> *Unfortunately, there is a years' worth of work we are trying to get organized into a coherent story. We have found holes which we feel need to be addressed... When you do not do it right up front, the rework is time consuming.*[130]

221. An internal PowerPoint dated August 19, 2007 listed the following complications with TVT-S and reflected problems with SIS for TVT-S known before 510(k) clearance: 1) insertion difficulties; 2) releasing difficulties; 3) fixation tips not staying in place; 4) bladder perforation; 5) excessive bleeding; 6) failures-tensioning. The presentation noted that the learning curve with TVT-S was much longer than originally anticipated, and that there was a "lack of right training", a "lack of local budgets leading to local decision for self-trained surgeons (CD, sales force)" and a "lack of clinical data."[131] In one presentation from Ethicon's Quality Board from approximately 2007, the first bullet-point recommendation to address Ethicon's known training concerns with the TVT-S was to "keep product in the market to train people."[132]

222. TVT-S was launched worldwide without a single long-term clinical study being conducted and only 5-weeks of human data.[133] About $2 million in TVT-S devices were sold in the first month during a "very limited controlled release."[134] Ethicon initially committed to six (6) surgeons (being used as clinical investigators) that Ethicon would conduct a post-launch RCT on the TVT-S.[135] Significantly, this included two European KOLs, Artibani and Carl Nilsson.[136] Dr. Artibani had previously signed on as a journal article author for Ethicon's TVT-S sheep study (which tested the pull-out force of the TVT-S versus the TVT), despite having no involvement in the actual study. Both Drs. Artibani and Nilsson initially agreed to be ambassadors for the TVT-S in marketing across Europe. These promised studies were not done by Ethicon based reportedly on cost and budget constraints.

223. Ethicon's internal documents dated June 20, 2006 showed concerns from these same two professors/surgeons about Ethicon "launching TVT SECUR with no clinical data (other than the 50 patients, 5 weeks to follow up)."[137] In fact, Dr. Artibani was quoted as being:

> *...surprised Ethicon did not learn the lesson from the launch of a prior product, MoniTorr...," when discussing the lack of clinical data. Harel Gadot, Ethicon's European Marketing Manager, then strongly recommended that Ethicon "find a way not to cancel completely the proposed RCT," since it was only after Ethicon*

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[130] ETH.MESH.00322464
[131] ETH.MESH.02105223
[132] ETH.MESH.00874445 p. 17
[133] ETH.MESH.00134795.
[134] Depo of Allison Brown, 9/12/13, 361:7-13.
[135] ETH.MESH.00134794
[136] ETH.MESH.03174256
[137] ETH.MESH.03172197. In addition, Board members at Ethicon had put in place an accelerated launch on the product and performing a clinical study would have caused a delay in the launch of the product. Deposition of Patrician Hojnoski, 4/16/13, 110:15-111:9.

assured its KOLs of its future RCT plans that these [two] professors got "back on board.[138]

224. As such, Mr. Gadot encouraged Ethicon to protect Johnson & Johnson's reputation and not cancel the RCT.[139] However, in September 2006, Ethicon decided *not* to perform a post launch RCT due to budget constraints.[140]

225. After Ethicon decided not to go forward with the randomized controlled trial (RCT), it immediately lost support for the TVT-S from Drs. Artibani and Nilsson.[141] However, it was already 510(k) cleared in 2005 for marketing in the United States. To date, several current and former Ethicon employees (including Medical Director Piet Hinoul)[142] have testified that Ethicon knew before the launch of the TVT-S that in some women there would be a severe foreign body response and recurrence, need for revision surgery, and dyspareunia. As noted above, perhaps the most obvious complication missing from the IFU is "pain", more specifically 'chronic pain'. This would include a lack of any reference to chronic pain, pelvic pain or other types of pain in the IFU caused by the TVT-S. To the contrary, the Ethicon IFU significantly underplayed the adverse event of mesh erosion and/or extrusion as "t*ransitory*" (*e.g.*, short-term, immediate) and made no mention of the fact that patients may need repeated/multiple surgeries to treat mesh complications.[143]

226. By November 6, 2006 there is an internal email from Mark Yale to David Robinson, Kevin Mahar, Dan Smith et al "Subject: TVT-S Complaint Review" with an internal review of reports with the withdrawal of the tape along with inserter, the issue first seen in the September 2005 Device Validation Study. The current reporting of a severe event is 1/1000 but not considered high enough to open a CAPA to address the problem:

> *Conducted TVT-S complaint review to look at issues specific to concerns of withdrawal of the tape along with inserter. Some general "anecdotal" concerns exists that there is potential high rate of occurrence with injuries related to device not coming off inserter during removal of the inserter, therefore the device is either moved from rest position or completely pulled out along with the inserter.*
>
> *This failure mode is covered in both design and application FMEA's---This is given a "8" severity and occurrence of 1/1000. In the design or dFEMA, the failure mode is established as "spring doesn't function" with the effect of "implant pulls out with inserter. This too is given a severity rating of an "8" with estimated frequency of 1/1000....*

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[138] ETH.MESH.03172197.
[139] *Id.*
[140] ETH.MESH.00314794 Page 4
[141] ETH.MESH.02105223 Slide 14 Bullet Number 10
[142] Piet Hinoul Depositions 4/5/12, 99:09; 4/6/12, 518:14-520:20; 6/26/13, 175:1-176:17, 184:18-22, 328:10-24.
[143] The 2008 Public Health Notification from the FDA characterized these complications as "rare," such that even if an implanter had reviewed the PHN, he would not have been fully informed about the occurrence rates or severity of any adverse events associated with the TVT-S.

> *Conclusion based on this review is that we do not yet have signs of an emerging issue with TVT-S which would warrant escalation of issue to PQI or CAPA based on trend or severity. While some issues have been uncovered in manufacturing process review which may impact spring alignment and may have led to difficult to remove issue, this investigation should be captured in NCR system and escalated to CAPA as necessary.*[144]

227. Incredibly, in the unpublished summary of the first 12-month human data available on the TVT-S (contained in an internal Clinical Study Report) performed by 6 of the top surgeons in the world who were all Ethicon KOLs (including Vince Lucente, Mickey Karram, Walter Artibani, and Carl Nilsson), there were a total of 51 adverse events reported in 32 out of 72 patients. One of the "safety conclusions" was that "[o]nly 69.4% subjects experienced no major device-related complications."[145] It went on to note "[o]nly 55% of the women reported no leak on self-assessment [the *subjective* cure rate]."[146] The summary concluded "[i]n the future, well planned randomized studies will have to be conducted in order to discern if the new single-incision procedures can achieve the same level of effectiveness as has been extensively shown with the TVT procedure and (with shorter follow-up) also with the TVT-O procedure. . . . As long as complications occur at the rate seen in this study . . . the single-incision procedure cannot be recommended as a first line treatment for [SUI]."[147]

228. In my opinion and based on my experience, expertise, and training, Ethicon withheld key information that was necessary for FDA to determine whether clearance of the 510(k) should occur based on the information known by Ethicon but not adequately presented to FDA in the 510(k). Based on Ethicon's claims of substantial equivalence to TVT and TVT-O, FDA would have had no way to independently evaluate the accuracy and viability of Ethicon's proposed draft TVT-S design for a mini sling, SIS and IFU. As a former Chief Medical Officer in ODE and as a physician with substantial labeling experience, this information should have been disclosed beginning with FDA and then to surgeons. However, even more importantly this information should have been considered and adequately studied by Ethicon before it launched TVT-S commercially. My opinion in this regard is bolstered by industry for example, the French National Authority for Health (HAS) conducted an evaluation of the safety and effectiveness of vaginally implanted mesh for the treatment of genital prolapse, finding that "[O]nly mesh materials validated by clinical trials should be used" and ultimately concluding that the use of mesh implants for transvaginal correction of genital prolapse remained a matter of clinical research.[148] Moreover, in June 2008, the National Institute for Health and Care Excellence (NICE) in the United Kingdom issued guidance on the use of mesh for treating vaginal wall prolapse. NICE noted that due to the risks of complications that can cause significant morbidity, "this procedure only should be used with special arrangements for clinical governance, consent and audit or research."[149] NICE stressed that patients should be provided with clear written

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[144] ETH.MESH.00329316
[145] ETH.MESH.02916609.
[146] ETH.MESH.02916610.
[147] ETH.MESH.02916611 (emphasis added).
[148] HAS French National Authority for Health —Evaluation of Mesh Implants Installed through the Vaginal Approach in the Treatment of Genital Prolapse (translated, French to English) November 2006.
[149] *Id.*

information to ensure they understand that there is uncertainty about long-term results and that there is a risk of complications, including sexual dysfunction and erosion into the vagina, that may require additional procedures.[150]

229. As a former Chief Medical Officer with ODE, it was particularly concerning to me that Ethicon proceeded to market the TVT-S and place it into the stream of commerce in spite of the alarming failure rates seen by the KOLs and other doctors, and in spite of limited testing on the safety and efficacy of the device.Clearly pre-market clinical studies or any long-term human clinical trials would have helped Ethicon and the FDA to determine whether the 510(k) as submitted (as well as the IFU) disclosed all known risks and new issues of safety and efficacy when compared to the cleared predicates. With accurate risk information, final decision about clearance of the 510(k) would have permitted the FDA to request additional information regarding clearance to consider new issues of safety and effectiveness. An adequate IFU and labeling for surgeons would have permitted them to determine whether to implant the TVT-S device rather than other available treatments for SUI including Ethicon's TVT and TVT-O. Finally, updated risk information for the labeling and the surgeon would have permitted a woman to determine for herself if she was agreeable to accept the risk of TVT-S for treatment of her symptoms of SUI, versus other available alternative treatments.

5. Ethicon Projected that with Aggressive Marketing TVT-SECUR Would Cannibalize Sales of TVT-O by 2008 and Classic TVT by 2009

230. Ethisorb was to be sourced out of Ethicon Hamburg, Germany and sent to Neuchatel for processing. Neuchatel and its supply chain was chosen to be used by Ethicon based on the "*tax savings*."[151] In terms of the marketing strategy for TVT-S after clearance and launch:

> *The targeting strategy for TVTx is to aggressively cannibalize our exiting TVT-O users followed by competitor obturator users in the first phase. This segment is the 'early adopters' they do not require clinical data unlike the current classic users who have not adopted obturator because of the lack of clinical data. The market model demonstrates very aggressive initial cannibalization of TVT O (2006-2008) followed by aggressive cannibalization of 'classic' from 2009. It is anticipated a 3-year follow would be available in 2009, which would assist in the conversion of the classic and retropubic customer segment.*[152]

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[150] In this regard, the Second International Urogynecological Association Grafts Roundtable conference was published on the subject of "[o]ptimizing safety and appropriateness of graft use in transvaginal pelvic reconstructive surgery," wherein the authors proposed that minimum standards should be demanded for new products prior to marketing, including "upfront clinical studies followed by a compulsory registry on the first 1,000 patients implanted. Ideally, manufacturers should support well-designed prospective (randomized) clinical trials that can support the claimed benefits of the new product." Slack M. A standardized description of graft-containing meshes and recommended steps before the introduction of medical devices for prolapse surgery (presented at 2nd IUGA Grafts Roundtable June 2010). *Int Urogynecol J* 2012; DOI 10.1007.

[151] ETH.MESH.01217673

[152] ETH.MESH.01217673

B. OPINIONS 4-7- POST-MARKET ISSUES WITH COMMERCIAL TVT-SECUR

OPINION # 4:

ETHICON'S MARKETING FOR TVT-S TARGETED SURGEONS WITHOUT REGARD AS TO PELVIC SURGERY EXPERIENCE, MINIMIZING DIFFICULTIES FOR PLACEMENT OF THE MINI SLING, INACCURATELY CALLING IT 'LESS INVASIVE' WHILE KNOWING THE PROCEDURE HAD A SIGNIFICANT SURGEON LEARNING CURVE, THE 'U' APPROACH WAS HARDER TO PERFORM THAN THE 'HAMMOCK', DIFFICULTIES WERE REPORTED WITHDRAWING THE INSERTER WITHOUT DISPLACING THE MINI SLING. ETHICON SELECTIVELY PROVIDED SOME SURGEONS WITH UPDATED INSTRUCTIONS AND SURGICAL TIPS WHILE ETHICON FAILED TO ADEQUATELY UPDATE ITS OWN LABEL, IFU AND MARKETING AND SALES FORCE TO WARN 'ALL' SURGEONS EQUALLY OF TVT-SECUR INCREASED RISKS COMPARED TO OTHER TREATMENT OPTIONS FOR SUI. FINALLY, ETHICON FAILED TO WARN SURGEONS ABOUT PATIENT RISKS FOR MESH EXTRUSION, EROSION, CHRONIC PAIN, WORSENING OF SYMTPOMS, DYSPAREUNIA AND NEED FOR ADDITIONAL SURGERY.

OPINION #5:

DESPITE ETHICON'S KNOWLEDGE OF POST-MARKET DIFFICULTIES FOR THE TVT-S SYSTEM , INCLUDING HIGH FAILURE RATE, BLADDER PERFORATIONS, COMPLAINTS FROM ITS OWN TRAINED KEY OPINION LEADERS (KOL), AND THAT EUROPEAN SURGEONS HAD STOPPED PERFORMING TVT-SECUR IN 2007 BASED ON UNACCEPTABLE RISKS, ETHICON CONTINUED TO MARKET TVT-SECUR IN THE UNITED STATES WITHOUT NOTIFYING SURGEONS OR PATIENTS ABOUT THE INCREASED RISKS. ETHICON DID NOT VOLUNTARILY CONDUCT POST-MARKET SURVEILLANCE STUDIES INCLUDING THE 522 STUDY IN ORDER TO UDPATE ITS AMERICAN LABEL, PHYSICIANS AND WOMEN WITH ACCURATE RISK INFORMATION.

OPINION #6:

BASED ON ETHICON'S MISREPRESENATIONS TO ITS SALES FORCE AND PHYSICIANS AS WELL AS THE FDA, INCLUDING ITS FAILURE TO CONSIDER AND DISCLOSE THAT THE MOST EXPERIENCED SURGEONS WITH TVT-S EXPERIENCED DIFFICULTIES AND

PREMATURE FAILURES WITH THE DEVICE, IMPLANTING SURGEONS WOULD NOT HAVE BEEN ABLE TO PROVIDE PATIENTS WITH AN ADEQUATE INFORMED CONSENT BASED ON KNOWLEDGE OF THE RISKS OF THE TVT-S PRODUCT AS A SIS MINI SLING FOR SUI.

OPINION #7:

SURGEONS RELIED ON THE KNOWLEDGE, SKILL AND EXPERIENCE OF ETHICON AS A MAJOR UNITED STATES MEDICAL DEVICE MANUFACTURER TO ADEQUATELY INFORM THEM OF THE RISKS FOR THE TVT-S AND PROVIDE PHYSICIANS WITH SAFE AND EFFECTIVE PRODUCTS TO PERMANENTLY IMPLANT IN WOMEN.

1. Ethicon Sold Commercial TVT-S with Inadequate Instructions for Use (IFU) and Warnings for Surgeons

231. The Instructions for Use (IFU) is a "how-to" guide which accompanies medical devices and can include the training materials (Surgical Manual) intended to teach the surgeon about the procedure and the risks. Sponsors of medical devices selling prescription devices have a non-delegable duty to provide physicians with adequate instructions for use as well as adequate warnings and precautions. (21 U.S.C. § 352(a)(f)(1)(2); 21 C.F.R. § 801.109). It is difficult for a surgeon in a sterile operating room with a patient on a surgical table to review the IFU which may be included in the medical device box. Usually there are materials provided to a surgeon outside the operating room by the salesforce and training sessions, medical meetings or in surgical manuals. All of these items are required to be truthful and accurate when generated by Ethicon and adequately inform and warn the physicians about the product benefits and risks.

232. In terms of the IFU for TVT-S, a significant problem is the understatement of the risk for Adverse Reactions listed on page 22 of its IFU. Here Ethicon continues the misleading use of the term "transitory" to describe the nature of the "foreign body response" that could result in erosion or extrusion; stated differently, Ethicon's statement to physicians is implying that the foreign body response associated with TVT-S would be 'temporary' or occur in the short-term (i.e. post-operative period) but not be permanent. Ethicon however *knew* this was inaccurate based on the reports it received for TVT-S.

233. Dr. Ming Chen, an Associate Medical Director for Ethicon, an individual responsible for post-market monitoring of physicians' and patients' complaints, responded to an email dated January 29, 2009 that referenced the language used in all the TVT IFUs on tape extrusion, exposure and erosion regarding *transitory* local irritation at the wound site which could result in extrusion, erosion, or inflammation. She stated "*Pardon me again, from what I see*

each day, these patients experiences are not 'transitory' at all."[153] As a former Chief Medical Officer in ODE and physician, I would have found this information vital as to the 'the permanence of the foreign body response and inflammatory reaction' for a TVT-S patient in assessing adequacy of the TVT-S' IFU and Ethicon's proposed intended use of treating symptoms of SUI. Ethicon executives knew that the statement and representation that the inflammatory response to TVT-S was transitory was misleading and inaccurate for surgeons as supported by Dr. Ming Chen's comments.

234. Dr. Charlotte Owens, who was the Medical Director from September 2003 until August of 2005, prepared a Clinical Expert Report ("CER") for the TVT-S[154] shortly before her departure from Ethicon. On November 2013, Dr. Owens testified that the potential complications in the CER were intended to be *similar* to what was included under Adverse Events in the IFU.[155] Ethicon's policy about what to include in the IFU and the CER under potential complications were fairly similar.[156] The draft of the CER prepared by Dr. Owens in August 2005 (before 510(k) clearance) listed a substantially greater number of potential and foreseeable complications than were listed in Ethicon's TVM tape IFUs or in particular the TVT-S IFU.

235. On October 3, 2005, a clinical protocol for a Pilot Study with TVT-S was finalized.[157] Contained within the Pilot Study was a list of Anticipated Adverse Device Effects. That list is identical to the potential complications listed in Dr. Owens' draft CER but which were missing from the IFU intended for physicians. On December 2, 2005, a final CER was signed by Dr. Marty Weisberg,[158] in which the Potential Complications had been changed from Dr. Owens' draft version but were now made to be identical to those contained in the TVT-S IFU. Dr. Owens testified that the only document that the public would receive warning of adverse events or potential complications was the IFU, and that the warnings contained in a CER or a clinical protocol for conducting a pilot study would only be seen by either the government regulatory employees or participant surgeons in the pilot study.[159] Dr. Owens testified that Ethicon could have included the complications in her draft CER and/or used in the Pilot Study protocol in the TVT-S IFU.[160]

236. The adverse reaction section for each of Ethicon's three (3) TVM TVT devices for SUI are almost identical, even though the three implant procedures, approaches and device design of Prolene tape devices are completely different.[161] As stated by Ethicon's Gary Borkes in his email to Dan Smith October 25, 2005, the TVT base for the new IFU for TVT-SECUR "the bar should properly not be "as good as" since the product is mature and "requirements for design control, risk assessment and other things that feed an IFU have changed since

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[153] ETH.MESH.04093117-ETH.MESH.04093118.
[154] ETH.MESH.01037447 Page 6.
[155] Deposition of Charlotte Owens 6.19.13 Page 178 Line 10-14.
[156] Deposition of Charlotte Owens 6.19.13 Page 179 Line 17-24.
[157] ETH.MESH.00538202 Page 24.
[158] ETH.MESH.03714002 Page 13.
[159] Deposition of Charlotte Owens, MD 6.19.13 Page 204 Line14-19.
[160] Deposition of Charlotte Owens MD 6.19.13 Page 212 Line 7-213 Line 1; 214 Line 5-13.
[161] ETH.MESH.05795622 at 16 (TVT Retropubic), ETH.MESH.03653529 at 7 (TVT-O); ETH.MESH.02340568 at 4 (TVT-S).

then."[162] Gary Borkes correctly told the team working on the IFU for TVT-S that the risk information should be updated from the past information of the older TVT and TVT-O Systems.

237. As a former Chief Medical Officer in ODE, I would have found the similarities of the static IFUs for such differing products over time to be unusual and not supporting that a company was carefully monitoring and updating its IFU information for physicians. The TVT family does share clearance for treatment of symptoms of SUI, but there are significant differences introduced for the SIS mini sling TVT-SECUR. Ethicon's approach to creating and continuing to use a similar IFU is odd, considering the histories of the three devices for SUI, the change in tape design of the TVT-S device, the changing medical literature for SUI, introduction of Ethisorb Dura Patch component, the different implant instructions needed for the surgeon to implant the TVT-S and the risks, (for example, the increased risks to legs for TVT-O, increased failure for TVT-S reported for patients). Such differences at a minimum should have triggered an internal response for Ethicon to voluntarily update its own IFUs and post-market information. Ethicon could have started with a common shared draft IFU but after product launch and continued post-market surveillance efforts by Ethicon the IFU must evolve and be updated to adequately address the risks for each TVM TVT product including TVT-S.

2. Ethicon Failed to Warn of Dyspareunia and Chronic Pelvic Pain for TVT-S

238. Also noticeably absent from the Adverse Reactions section was mention of the reporting of dyspareunia and chronic pelvic pain, which were known adverse reactions according to internal Ethicon documents.[163] Dr. David Robinson, Ethicon's former Medical Director, testified that these were known adverse reactions with the TVT-S.[164] Though Dr. Robinson was aware that erosion was a possible adverse reaction to the TVT-S and that possible complications associated with the TVT-S included multiple surgeries to treat the resulting erosion, it was information not included in the TVT-S IFU.[165] The IFU did not address the potential difficulty removing the mesh after tissue ingrowth. Thus, despite the known non-delegable duty for Ethicon to provide an adequate IFU for physicians in terms of compliance with the Act, Ethicon's IFU was inadequate when it provided vague/nonspecific adverse reactions that did not capture the TVT-S post-market performance.

239. As a former Chief Medical Officer in ODE and physician, I would have found an adequate IFU with updated post-market risk information clinically helpful as well as required by Ethicon. Because Ethicon did not disclose this information in the IFU (or for that matter in its "tips & tricks" or other training materials), the IFU is inadequate and did not sufficiently apprise physicians and patients of the risks associated with the device. With this inadequate risk information, surgeons would not have been able to provide patients with an opportunity

[162] ETH.MESH.00526111

[163] ETH.MESH.04081189-ETH.MESH.04081190 (memo noting Ethicon's IFU failed to warn its patients of the TVT risks, particularly the dangers of erosion and painful sexual activity).

[164] David Robinson Dep. at 251:7-12. In addition to Dr. Robinson's testimony, Ethicon's internal Risk Assessment on the TVT-S noted an unexpected or ineffective interaction between the mesh and tissue could lead to wound dehiscence, among other complications.

[165] Deposition of David Robinson, M.D 7.24.13, 355:16-356:8.

to have an adequate informed consent discussion about implanting TVT-S. The lack of adequate risk information specific to TVT-S would also have denied the physician the ability to determine whether or not to implant TVT-S versus any of the other available devices for SUI, including Ethicon's TVT or TVT-O, even though Ethicon's internal documents and the published medical literature reflects these predicate devices were associated with less adverse events and failures.

3. Ethicon Inaccurately Marketed TVT-S as "Tension Free"

240. In addition, the IFU stated that the TVT-S like TVT and TVT-O was "tension-free;" however, this is not the case for TVT-S. Ethicon found that too much tension applied to the tape may cause temporary or permanent lower urinary tract obstruction. To the contrary, not enough tension or incorrect placement would result in incomplete or no relief from urinary incontinence. One of Ethicon's Key Opinion Leaders ("KOLs") gave his opinion that "the IFU is fundamentally misleading" and "tension-free, tension-less and placement with no tension are complete misnomers."[166] This email and others[167] outline a significant difference between what Dan Smith was telling Dr. Robinson and others in the US, and information Dr. Aran Maree (Ethicon's Medical Director for Australia) was learning from discussions with the very same people.[168]

241. As early as mid-2007, KOLs who had been implanting the TVT-S product were experiencing high failure rates—in part, due to a variety of defects with the TVT-S as identified in the medical literature and internal documents, and partially because the IFU was unclear regarding the appropriate surgical technique. On November 2, 2007, Dr. Maree noted:

> *It is my understanding that some suggestions had come out in the form of (i) increased tension required with this mesh with 'pillowing of peri-urethral tissues required,' (which is quite the opposite of TVT-O recommendations), as well as (ii) new tips and tricks to avoid dislodging the device when removing the inserters and (iii) new tips for minimal dissection when introducing the product. We also discussed the fact that at this time some or all of these suggested changes may not be incorporated into the [IFU] or technical training material.*[169]

242. Despite these known concerns with the surgical implantation technique of the TVT-S that were not reflected in the IFU, Ethicon chose to never voluntarily update its IFU.

4. Ethicon Marketed TVT-S Widely To All Surgeons Without Regard for Experience

243. Despite Ethicon's receiving complaints from its own KOLs, surgeons, and scientific literature reporting higher complication and failure rates (and eventually higher rates of mesh erosion and extrusion), Ethicon's aggressive marketing efforts continued to expedite

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[166] ETH.MESH.00327061-ETH.MESH.00327063.
[167] ETH.MESH.06051155.
[168] ETH.MESH.00311792 at 2.
[169] ETH. MESH.00312180.

wide-spread commercialization of TVT-S in the United States. It had its sales force knowingly market the TVT-S to surgeons who did not specialize in implanting such technically difficult devices as "less invasive." Ethicon was aware that even the most experienced surgeons with the TVT-S were reporting difficulty obtaining successful results with the device. For example, a March 14, 2007 email sent by Dr. David Robinson to Dr. Axel Arnaud acknowledged that the first human use study (referenced above) taught "that the learning curve is longer than we thought, mesh tensioning is different than kits with sheaths and that following the IFU is important"[170] During a June 18, 2008 interview, KOL Carl Nilsson[171] stated that the learning curve for him with the TVT-S was "100 patients before he was very good with very dry results."[172]

244. In 2007, Ethicon's Quality Board conducted an analysis of the complaints on that point. In this meeting, a PowerPoint[173] there was a "lessons learned" slide,[174] that stated:

- Carefully consider launching a competitor to our own very successful products
- Consider not carrying out a first human use trial and launching a product at the same time
    - The learnings from trial should be gathered, digested and device adjusted accordingly before launch
- Use caution when offering a device that can be used in more than one way
- Do not underestimate the learning curve.[175]

5. Ethicon Marketed TVT Universal System Despite Differences of Implantation Technique and Increased Risk of Failure with the "U" Approach

245. The TVT-S was also called a TVT Universal System and was marketed to surgeons as able to be implanted by two different implant techniques based on surgeon preference: "U" position or the "Hammock" position. However, the SIS mini TVT-S implantation techniques were drastically different used for either the standard TVT U approach or the TVT-O hammock. Dr. Aran Maree testified that the TVT-S was a product that had either a substantially new technique or was significantly modified from its predecessor products.[176]

246. In 2007, Dr. Robinson stated in an email: "[s]ince SECUR clearly is a sling 'unto itself' as far as techniques go, much relearning had to occur to gain success in the US and particularly in Europe."[177] As a former Chief Medical Officer in ODE, I would have found such lack of clinical disclosure by Ethicon in its 510(k) and difference in implantation techniques to be significant when a reviewer was evaluating the device 510(k). Dr. Herrera, a trained

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[170] ETH.MESH.03922618

[171] Notably, he co-authored several of the 3, 5, 7, and 17 year studies on the TVT-Retropubic with Professor Ulmsten.

[172] ETH.MESH.04048515 at 3. He also said in this interview that he would never use laser cut mesh.

[173] ETH.MESH.00874445.

[174] *Id.*

[175] *Id.*

[176] Aran Maree Depo, 7.22.13, 137:8-16. This is significant because the TVT-S was marketed to doctors and physicians around the world as a new and improved TVT.

[177] ETH.MESH.00832210-ETH.MESH.00832214; ETH.MESH.00642328.

urologist and ODE medical officer did identify that the TVT-SECUR mini sling insertion procedure was totally different than either of the prior TVT procedures. His concerns in September 2005 about the ability of a physicians to insert an 8cm mini sling as described by Ethicon in the 510(k) prompted his request to Dr. Lerner that Ethicon perform a clinical trial with 12 month data. The study was not performed after Ethicon identified a mini tape predicate, with no statement from Dr. Herrera that his original concerns were incorrect or that data was not necessary to support "effectiveness". Despite Ethicon's ability to obtain 510(k) clearance following identification of the Gyne Ideas Mini Tape 510(k), there was nothing that would have prevented Ethicon as a responsible manufacturer from performing a clinical trial, even with the commercial device or under a FDA approved IDE to obtain robust 12 month data as suggested by Dr. Herrera, to ensure the adequacy of the design, safety of women and update its risk information in its IFU, labeling and marketing.

247. As discussed above, in its mandatory signed 'truthful and accuracy statement', Ethicon certified that the information provided to FDA in the 510(k) was truthful and accurate and left out no material facts about the TVT-SECUR. Despite Ethicon's certification that all material facts were provided to FDA, that does not appear accurate. Despite Ethicon's statement to FDA that it had determined that TVT-SECUR was substantially equivalent to TVT and TVT-O Systems, the TVT-SECUR mini sling was cleared not based on either of the TVT systems but on the Gyne Idea's Mini tape. Dr. Herrera had pointed out the significant differences of the TVT-SECUR from the two TVT Systems in his September 2005 Clinical Review and requested that Ethicon identify a cleared predicate min sling with a similar insertion procedure. Therefore, Ethicon's claim in its 510(k) that TVT-SECUR was only a 'modification' of TVT and TVT-O was potentially inaccurate and misleading.

6. Ethicon Marketed TVT-S Without Conducting Adequate Study of the Kit's Overall Component Design and Acceptability of Performance for Surgeons

248. One study prepared by some of Ethicon's KOLs stated there was a risk of erosion related to the sharpness of the inserter:

> *...was an increased incidence of mesh exposure in the TVT-S group. Although the etiology of this complication is unclear, we theorize that the sharper edges of the TVT-S introducer potentially create more trauma to the vaginal epithelium and may result in high erosion rates.*[178]

249. Ethicon's 510(k) indicated that the TVT-SECUR relied on the use of "metal needles attached to the sling ends" and shared the use of metal needles with TVT System. Therefore, metal needles as described in the 510(k) imply the ability to poke, stick, lacerate when placed into the pelvis, even for a mini sling and single incision. The sharper TVT-S introducer potentially was able to create trauma to the pelvis structures and the vaginal epithelium and may of itself be able to contribute to the high erosion rates for TVT.[179] Ethicon did not investigate the possible risk that the sharper edges of the TVT-S introducer might subject patients to greater tissue trauma that would predispose them to erosions.

[178] ETH.MESH.04474756–ETH.MESH.04474760.
[179] ETH.MESH.04474756–ETH.MESH.04474760.

Ethicon did not investigate or warn about the risks of the sharp inserters in terms of the potential for injury to structures and organs with insertion as well as removal, including tearing and laceration of muscle. In addition, this information about the risk of the design of the inserters was not adequately addressed in the 510(k) application.

250. In 2007, Ethicon's Quality Board conducted an analysis of the complaints that it had received at that point. Ethicon knew that the two most significant US complaints by surgeons from insertion process were: (1) the implant pulls out with the inserter; and (2) that the inserter itself was difficult to remove.[180] These were complaints seen in the initial Design Validation Study- Part 1 and 2 before 510(k) clearance. In this internal meeting, a PowerPoint[181] was shown that highlighted the challenges already identified for the TVT-S System:

- Reinventing procedure (positions)
- Not simpler- longer learning curve
- Release mechanism
- Release techniques
- Slight increase in bleeding
- Tape tensioning!!! Without retention!!!

251. In the presentation, there was a slide titled "lessons learned", [182] which stated:

- Carefully consider launching a competitor to our own very successful products
- Consider not carrying out a first human use trial and launching a product at the same time
    - The learnings from trial should be gathered, digested and device adjusted accordingly before launch
- Use caution when offering a device that can be used in more than one way
- Do not underestimate the learning curve.

7. Ethicon Relied on An Engineer, Dan Smith, to Create a TVT-S Cookbook for Implanting Surgeons, Providing Additional "Tips and Tricks" to Only Some Selected Surgeons

252. In December 2006, Dr. Axel Arnaud (Ethicon Medical Affairs Director [Europe, Middle East, and Africa]) suggested to Dan Smith (engineer from R&D/co-inventor of the TVT-S) and Dr. Robinson the need for a "TVT-S cookbook," which would reflect changes to the surgical procedures that were outlined in the IFU. His reasoning was that surgeons, even KOLs:

> *...who have been correctly trained and who have passed the learning phase, are raising concerns about the efficacy of the TVT SECUR . . . They are asking for clear recommendations about the way to perform the procedure, in particular*

[180] ETH.MESH.06051286 at 5 & 25.
[181] ETH.MESH.00874445.
[182] *Id.*

about the size of the dissection, the tension to be given to the tape and the way to perform a cough test.[183]

253. Despite the importance of the new information for surgeons already trained on the TVT SECUR, none of these implant "tips" were added by Ethicon to its TVT-S IFU to be shared and available for all implanting surgeons.[51]

254. Curiously, Dan Smith, the R&D Engineer for the Project but without any clinical training or experience implanting TVT-S devices in living patients, expressed his adamant disagreement with Dr. Arnaud, a clinician, finding "the cook book" to be far too long with too much information in it. Dr. Arnaud emphasized that Ethicon could not "ignore that some surgeons who have been able in the past to successfully perform TVT and TVT-O are now struggling to achieve the same results with SECUR." Dr. Arnaud continued that he wished "the solution would just be to tell them to go back to their homework, but I am not sure it is the best one."[184] In the same email, Dr. Robinson concluded that "it is just as clear that we are having some type of training problems and in order to prevent wide spread negative talk, I think we must take palliative steps quickly."[185]

255. Rather than revise the IFU and training programs, even though it was thought necessary, Ethicon decided to offer "cookbooks" and "procedural pearls" as a temporary solution. Of significance, these "tips & tricks" were only to be provided to surgeons who specifically requested training. The tips and tricks were never sent out widely to all surgeons implanting the device, added as an update to the IFU or given to salesforce to provide directly to all surgeons implanting the TVT-S. The tips and tricks were not sent to implanting surgeons as a communication including as a Dear Doctor Letter. As a former Chief Medical Officer in ODE, it would have been of significant concern to me that Ethicon selectively offered additional safety information only to certain surgeons to supplement its inadequate IFU. Even besides the IFU, other vehicles to circulate safety information would have included Ethicon's use of its own salesforce as well as Doctor Letters, post-market studies and training. These "tips & tricks" should have been incorporated into the IFU no later than 2008, and additional training materials voluntarily sent to all surgeons/hospitals which had purchased the TVT-S.

8. Ethicon Knew European Surgeons Abandoning TVT-S in 2007 Based on Unacceptable Risks and Failures But Failed to Notify the FDA or United States Physicians

256. In a May 17, 2007 presentation to Ethicon employees, Dr. Axel Arnaud noted under "Key Issues in Europe" that "[s]ome key experts and non-experts are disappointed" and "[k]ey experts are abandoning the procedure." One slide was on the "Future of Europe," where he noted that the "advantages of conventional TVTs are insufficient for accepting more failures."[186] Thus, while Ethicon was well aware of the need for retraining (or heightened

[183] ETH.MESH.00519479.
[184] ETH.MESH.01784428 at 2-3.
[185] ETH.MESH.01784428 at 1.
[186] ETH.MESH.00572598.

training standards), it decided again to be selective and not offer retraining universally to all surgeons.[187]

257. On August 19, 2007, the Worldwide Marketing Team provided a presentation on the "Incontinence Platform,"[188] showing the following reported complications with the TVT-S:

- Insertion difficulties
- Releasing difficulties
- Fixation tips not staying in place
- Bladder Perforation
- Excessive Bleeding
- Failures- Tensioning
- Not well defined "cookbook" procedure leads to difference in the technique between surgeons

[Of note, the presentation stated follow-up actions include establishing a procedural "cookbook" which was "ready and distributed," "emphasize importance of hands-on training," "establish clinical data," and conduct an "experts meeting"].

258. In addition to these complications, the presentation noted that the learning curve is much longer than originally anticipated, lack of right training and a lack of clinical data, such that KOLs are not supporting the TVT-S. As a former Chief Medical Officer in ODE and Medical Officer in OHA, it is apparent that Ethicon did not provide FDA with a complete and accurate post-market picture as to the risks reported for the TVT-SECUR. Ethicon continued to sell the TVT-SECUR in the United States despite offering safer alternative products and no unique medical benefit for its availability for patients. By May 17, 2007 Ethicon knew the procedure was being abandoned in Europe. By August 19, 2007 the Worldwide Marketing Team could create a laundry list of serious problems associated with the TVT-SECUR. Ethicon had the option to discontinue sales and withdraw the product from the United States market, notify physicians of the risks for already implanted patients. The option for Ethicon of behaving responsibly by withdrawing the product, prevented any additional patients from being needlessly implanted with TVT-SECUR and harmed. It also permitted Ethicon to re-examine the adequacy of the device design and fulfillment of the performance requirements. With additional testing and design the product may be able to be corrected to perform as described in the cleared 510(k). However, when Ethicon continued to sell a product to be permanently implanted in women for SUI that it knew was defective, it was knowingly marketing a device that was not safe and effective and did not perform as cleared for marketing by the FDA. The device which Ethicon continued to sell in the United States as the TVT-SECUR with a premature risk of failure and patient injury and inadequate and misleading labeling was adulterated and misbranded.

259. Dr. Maree placed a "quality block" on the TVT-S in Australia in New Zealand in October 2007,[189] after inquiring into potential issues associated with the TVT-S in the earlier part of

[187] ETH.MESH.17662610-ETH.MESH.17662615 ("Professional education...should not be offered to everyone, only qualified surgeons who have the case load as well as the commitment to utilize the product. Remember an event is only as good as the follow-up and ROI. Please keep this in mind when utilizing professional education.")
[188] ETH.MESH.02105223.

2007. The "quality block" prohibited the TVT-S from being released from the warehouse.[190] A few weeks later, the decision was made to withdraw the TVT-S from the Australian market. None of this information about discontinuation of sales in Australia in 2007 was provided to Untied States physicians or the FDA. Writing to Catherine Beath in the United States, Dr. Maree stated:

> *We feel that withdrawing the product from the market here is currently the most appropriate action for Australia. We believe this to be appropriate until we are confident that a modified technique, appropriately documented and tested by way of clinical study, can be taught to our surgeons and will lead to optimal patient outcomes with this product.*[191]

260. In March 2008, a Dear Doctor Letter was mailed to Australian surgeons,[192] and because of this, the surgeons stopped using the product and shipped the remaining stock back to Ethicon.[193] No retraining was ever done on the TVT-S in Australia.[194] No Dear Doctor Letter was sent to United States physicians and the product continued to be marketed in the United States.

261. Ethicon's continued representations to the FDA, and the public, about the performance of the TVT-S after launch and in 2007 was misleading. Ethicon did not truthfully and accurately disclose this known post-market information to FDA, United States physicians or the public.

i. Failure rates:

262. As an alternative to the RCT that was initially promised to various KOLs, Ethicon decided to start "TVT World" as a long-term clinical/patient reported outcome database on the use of the GYNECARE TVT systems for SUI.[195] GYNECARE World was clearly designed to overcome Ethicon's failure to do any RCTs because of budget constraints and the noise around the launch with no clinical data. The first patient enrolled on February 16, 2007. Out of all of the 1235 procedures registered, 53.6% were listed as TVT-S patients.[196] By January 2009, there were 30 sites in 9 different countries, the largest of which were in the US.[197] In addition, in January 2009, there were also 5 TVT-S studies going on. [198] They were:

- Karram Multi-center RCT: SECUR v. TVT (TVT-S:130 of 280 patients)
- Rosenblatt RCT: SECUR v. TVT-O (TVT-S: 89 of 128)

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[189] Dep. of Aran Maree 7.22.2013 at 189:14-190:22.
[190] *Id.*
[191] ETH.MESH.00326842 at 4.
[192] ETH.MESH.05404976.
[193] Dep. of Aran Maree 7.22.13 at 265:4-18.
[194] ETH.MESH.04127331.
[195] ETH.MESH.00134794 Slide 6
[196] ETH.MESH.00134794 Slide 7
[197] ETH.MESH. 00134794Slide 8
[198] ETH.MESH.00134794 Slide 12

- Roovers: Multi-center RCT: TVT-SECUR v. TVT-O
  - 6 month interim results: abstracts to ICS in 2009
- Woods: Feasibility in Office 20/20 (all TVT-S patients)
- Khandwala: In-office evaluation 14/20

263. The TVT World Registry was discontinued at end of March 2009 as a result of the TVT-S losing market share and failure to meet expectations. [199] This move created a significant savings for Ethicon.

264. From a review of the internal documentation for the TVT World Registry, the primary goal of the registry was to provide clinical data to support Ethicon's marketing. As a former Chief Medical Officer in ODE, I would have found the biases and shortcomings in the collection of post market information another opportunity missed by Ethicon to obtain robust post-market data as to outcome of patients for treatment of SUI. The flaws in the capturing of the data will significantly underestimate the true performance (success/failure outcomes for treatment for SUI rates) and risk for TVT-S.

265. In addition to the significant high failure rates reported soon after the launch of the TVT-S, one study documented up to a 42% failure rate with the TVT-S, concluding that:

> *Our experience shows that despite its good short-term efficacy, TVT-SECUR is associated with a high recurrence rate of SUI. Therefore, TVT-SECUR does not seem appropriate for SUI first-line management in women.*[200]

266. Ethicon's documents showed that surgeons were experiencing "high 'failure' rates across multiple centers [sic]" as of 2007.[201] Several surgeons attempted to modify their surgical technique but still experienced failures. On October 25, 2007, Dr. Maree attributed the failures to the product having been "launched as a substitute for TVT-O without enough clinical data to justify the roll-out," and that the original training program did not result in "competency in device insertion."[202] In November 2007, Catherine Beath (VP of Regulatory Affairs at Ethicon) sent an internal email summarizing 6-week "success rates" for 3 KOLs:

> Our initial inquiries indicate that the following are roughly the 6-week success rates for these three surgeons:
>
> Prof Malcolm Frazer Performed: ~ 20 cases, Failure: ~13 cases (he has performed about 700 TVT cases over the years)
>
> Dr Bruce Farnsworth Performed: ~ 20 + cases, Failure: ~6 cases
>
> Prof Marcus Carey Performed: ~ 20 cases, Failure: "lots of early failures" (8 at least and still counting) , awaiting a final number from this surgeon
>
> All of these surgeons have indicated that their success rate with TVT Secur is substantially below their success rates with TVT-O [203]

[199] ETH.MESH.00134794 Slides 13 and 14.
[200] Cornu JN, Ripe P, Peyrat L, Ciofu C, Cussenot 0, and Haab F. (2010) "Midterm prospective evaluation of TVT-SECUR reveals high failure rate." *Eur Urol.* 2010 Jul; 58(1):157-61.
[201] ETH.MESH.00642330-ETH.MESH.00642331.
[202] *Id.*
[203] ETH.MESH.00312179-ETH.MESH.00312182.

267. In addition, Dr. Lucente, a well-renowned surgeon and noted Ethicon KOL, was also experiencing high failure rates. Within the 6-week follow-up of his first 25 patients, about 40% experienced SUI.[204] Below is a chart showing Dr. Lucente's experience after 6-week follow-up:

ETHICON Women's Health & Urology

TVT SECUR

Dr. Lucente experience @ 6 weeks follow-up

	First 25 patients	First 77 patients	All 136 patients (updated)	Last 25 patients (updated)
No SUI	15 (60%)	53 (68.8%)	105 (77.2%)	23 (92%)
SUI	10 (40%)	24 (31.2%)	31 (22.8%)	2 (8%)
De novo OAB	3 (25%)	8 (26.7%)	4 (2.9%)	1 (4%)
Voiding dysfunction	1 (4%)	2 (2.6%)	2 (1.5%)	0
Erosion/ Exposure	1 (4%)	1 (1.3%)	1 (0.93%)	0
Pain	0	1 (1.3%)	3 (2.2%)	0

268. It is interesting to note that Dr. Lucente had to subsequently modify his own technique from the original Ethicon-provided training in order to help to improve his results.[205] Upon learning about Dr. Lucente's failure rates, Dr. Maree stated "…it is not surprising that we may have similar or higher failure rates here [Australia]. This is very different to the QA databased numbers sent through from the 'reported' complaint rates divided by the USA sales earlier on."[206]

269. In 2010, an internal email from Dan Smith, the device's co-inventor, stated "TVT SECUR was considered a failure and did not warrant line extensions."[207] However, only after the FDA's 522 Order in 2012 did Ethicon officially elect to de-commercialize the device and discontinue sales.

270. In 2014, the Cochrane Collaboration (arguably the 'gold standard' for summaries on studies and scientific literature) analyzed various single-incision operations for urinary incontinence in women by interpreting the results of a number of RCTs and quasi-RCTs. Despite having already been withdrawn from clinical use at the time of the study, the report included the TVT-S "so that level 1a data" would be "available in the literature to confirm its lack of efficacy."[32] The report included a comparison of several mini-slings, including the TVT-S and MiniArc, among others. Even though no ultimate conclusion was reached on the efficacy or safety of any SIS other than the TVT-S, SISs were noted to result in higher incontinence rates compared with inside-out transobturator slings (30% vs 11%). However, the adverse event profile was noted to be significantly worse, specifically consisting of higher rates of vaginal mesh exposure, erosion, and operative blood loss. Significantly, the overall results of the studies demonstrated the TVT-S was "***considerably inferior*** to retropubic and inside-out transobturator slings." The authors of the study concluded that "TVT-SECUR is inferior to standard mid-urethral slings for the treatment of women with stress incontinence and has already been withdrawn from clinical use."

[204] ETH.MESH.02105223.
[205] ETH.MESH.00642325-ETH.MESH.00642331.
[206] ETH.MESH.03845446-ETH.MESH.03845449.
[207] ETH.MESH.06927248-ETH.MESH.06927249.

271. Recent additional studies have also confirmed the inferior cure rates associated with the TVT-S when compared with the TVT-O.[208] Of note, Dr. Carl Nilsson, the same Ethicon KOL who co-authored various studies on the TVT who was set to be Ethicon's "ambassador" for the TVT-S, wrote a recent article calling for clinical studies on new medical devices:[209]

> *Recent history includes the launch and withdrawal of many modifications and copies of the TVT procedure, which shows that any variation of a procedure needs its own thorough clinical testing before it can be accepted for common use. The surprisingly high rates of complications such as bladder perforation and post-operative voiding problems seen in more recent reports compared with the rates seen in the initial ones from the Nordic countries emphasizes the need for proper training and adherence to the standardized performance of the operation in order to avoid complications and poorer performance. It is a waste of both public and private resources to launch poorly documented new treatment concepts and it is especially wrong for the women suffering from [SUI] to become the subjects of experimental efforts without ethical approval and written informed consent.*[210]

9. Internal Ethicon Documents Reflect the Recommendation for the Incision Size and Depth Listed in the IFU Had Not Been Accurately Determined Unnecessarily Exposing Patients to a Greater Risk of Mesh Erosion/Extrusion and Failure

272. Ethicon's IFU reflected the need for a 1.0-1.5 cm incision size;[211] however, internal documents show there was no agreement on the depth or amount of dissection of the TVT-S' surgical incision.[212]

273. Dr. Menachem Neuman, on January 20, 2007, after receiving a request to share TVT-S "success stories," wrote:

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[208] *See* Hota, Lekha S., MD, *et al.*, TVT-SECUR (Hammock) Versus TVT-Obturator: A Randomized Trial of Suburethral Sling Operative Procedures. *Female Pelvic Med Reconstr Surg.* 2012, Jan-Feb; 18(1): 41-45. DOI: 10.1097/SPV.0b013e31823bdbcf (47% cure rate for TVT-Svs. 91% for TVT-0); *see also* Maslow K. Randomized clinical trial comparing TVT SECUR system and trans vaginal obturator tape for the surgical management of stress urinary incontinence. *Int Urogynecol J* (2014) 25:909-914. (63% cure rate for TVT-S and 86% cure rate for TVT-O); Mostafa A, Single-Incision Mini-Slings Versus Standard Midurethral Slings in Surgical Management of Female Stress Urinary Incontinence: An Updated Systematic Review and Meta-analysis of Effectiveness and Complications; *European Urology*, 2014; 402-427 ("This meta-analysis shows that, excluding TVT-Secur, there was no evidence of significant differences in patient-reported and objective cure between currently used SIMS and SMUS at midterm follow-up while associated with more favorable recovery time.").

[209] Nilsson, *Creating a gold standard surgical procedure: the development and implantation of TVT*, Int. Urogynecol. J. (2015) 26:467-269.

[210] *Id.*

[211] ETH.MESH.02340568-ETH.MESH.02340590.

[212] ETH.MESH.03752501-03752506; ETH.MESH.07039973- 07039975 (stating that the incision size should be 1.2-1.5 cm).

- *It would be necessary for a surgeon in training to undergo 5 training operations with Neuman to become a "flying surgeon" (Preceptor). Thereafter, the "flying surgeon" would need an additional 20 to 30 operations to form the "inner-country" pyramid of homeland trainers.*
- *Surgeons who are more familiar with TVT-O will require more training for the TVT-S in order to overcome the "dragged bad habits" from the former operations to the new one. There are special differences between the TVT-O and TVT-S and those should be addressed to and respected if high cure rates and low complication rates are desired.*[213]

274. He attached his preceding steps,[214] which were his recommendations to the TVT-S IFU and how surgeons needed to have the proper technique; namely, that it was better if the incision size was closer to or greater than 1.5 cm.

275. The key technical points, received by Ethicon employees on July 26, 2007, reflected that the incision size "should be made slightly larger than with conventional slings (closer to 1.5 cm) and of full thickness, to allow mesh to lie flat underneath urethra. This may reduce risk of incision disruption and mesh exposure."[215] A little over a month later, in August 2007, Dr. Sepulveda, one of Ethicon's KOLs, presented a copy of his critical steps where he wrote that "[a]n incision of 1.5 – 2.0 cm . . . was required."[216] And just two years later, in one of Dr. Sepulveda's training sessions he taught that a vaginal incision size of +/- 2 cm was necessary.[217]

276. Internal documents reflect Ethicon's awareness as early as 2007 that the incision size of the TVT-S reflected in the IFU was an issue; however, Ethicon never once updated the IFU. This is significant because it demonstrates that Ethicon not only failed to disclose all of this information to the FDA in the 510(k), but continued to fail to disclose this significant procedure information to all surgeons using this device, and failed to treat the IFU as the "living document" it is intended to be.

10. Ethicon Failed to Warn Patients of Risk in Patient Brochures and Provided Patients with Misleading Information About TVT-S.

277. Ethicon intended for the information contained within its 'patient brochure' for the information to be provided to the patient.[218] It is reasonable (as well as required by the Act and regulations) for patients to expect that the information that was intended for them, such as patient brochures and advertisements, were truthful and accurate and that they should be able to rely on those materials.[219] One of the items Ethicon's regulatory personnel was

[213] ETH.MESH.02320486.
[214] ETH.MESH.02320488.
[215] ETH.MESH.17666960-ETH.MESH.17666969
[216] ETH.MESH.10226089
[217] ETH.MESH.02596703.
[218] Deposition of Patricia Hojnoski April 16 2013.
[219] Deposition of Patricia Hojnoski April 17 2013.

considering was to "[d]evelop creative regulatory strategies which will support the desired claims, but will have the lowest regulatory hurdles possible."[220]

278. Below is a history of the brochures:

- Unknown Date: Brochure published unknown date featuring the "Bonnie Blair" including the TVT SECUR[221]
  - The word "rare" is removed from the brochure before the word "injury" in describing the risks for this brochure
- May 31, 2007: A brochure published approved by Ethicon on 5.31.07 with the TVT SECUR.[222]
  - The brochure states: "98% of women treated with GYNECARE TVT are still dry or report significantly less leakage 7 years after the treatment"[223]
- December 10, 2008: Brochure approved is the 2nd marketing brochure in which TVT-SECUR is included.[224]
  - The language in the brochure slightly lowers the success rate from the May 2007 brochure from 98% to 97% in the 12.08 brochure: "97% of women surveyed following treatment with GYNECARE TVT were still dry or had significantly less leakage 11 years later.[225]
    - However, there are not footnotes in this 12.08 brochure similar to the 5.07 brochure regarding this statement about the success.
    - In the 5.07 brochure behind the claim of 98% success rate it had a footnote which read: "81.3% of women remained dry and an additional 16.3% of women remained significantly improved."

C. OPINION #8- POST MARKET 522 ORDER:

OPINION #8

FDA ISSUED A 522 ORDER TO COMPEL ETHICON TO OBTAIN POST-MARKET PERFORMANCE INFORMATION FOR TVT-SECUR MINI SLING TO UDPATE THE LABEL. ETHICON'S MANAGEMENT HOWEVER CHOSE TO DECOMMERCIALIZE (STOP SALES) TVT-SECUR. ITS ACTION HALTED THE 522 PROCESS AND ETHICON DID NOT COMMIT TO OBTAINING ANY OTHER POST-MARKET PERFORMANCE INFORMATION FOR WOMEN ALREADY IMPLANTED. AFTER STOPPING SALES OF TVT-SECUR ETHICON CONTINUED NOT TO ADEQUATELY NOTIFY PHYSICIANS OR WOMEN ABOUT THE RISKS ASSOCIATED WITH TVT-SECUR.

[220] ETH.MESH.07931874 Page 1.
[221] ETH.MESH.00764748.
[222] ETH.MESH.08003263
[223] ETH.MESH.08003263 Page 11
[224] ETH.MESH.08003279
[225] ETH.MESH.08003279 Page 13

VII. PHYSICIANS BEGAN TO QUESTION THE LACK OF ADEQUATE CLINICAL DATA FOR PELVIC MESH

A. DR. OSTERGARD, AMERICAN UROGYNECOLOGY SOCIETY (AUGS), EXPRESSED HIS CONCERN OVER LACK OF 'LONG-TERM SAFETY & EFFICACY DATA' AND ADEQUATE FDA OVERSIGHT OF TRANSVAGINAL MESH

279. Ethicon would have been aware that Dr. Donald Ostergard, a founding member of the American Urogynecology Society (AUGS) at the 2006 AUGS meeting presented his concerns about the FDA's need for greater oversight for new devices. He provided examples of recent implants/devices which have led to disappointing outcomes, including the ProteGen pubourethral sling with suspension by bone anchors. He pointed out:

> *Without adequate information, the possibility that associated problems will not be identified until a new device has been used on hundreds or possibly thousands of women is significantly increased.*

B. ACOG'S PRACTICE BULLETIN #79 FOR PELVIC ORGAN PROLAPSE CALLS 'PELVIC FLOOR MESH REPAIR PROCEDURE KITS' "*EXPERIMENTAL*"

280. On February 5, 2007 American College of Obstetricians and Gynecologists (ACOG) sent out a message from Susan Hobson, MD., GYN-section chair regarding mesh POP to its members. The subject was "Important ACOG statement on pelvic floor mesh kits." The ACOG letter was intended to bring to a physician's attention ACOG's newly released Practice Bulletin on POP, and specifically about ACOG's concerns for the pelvic floor mesh kits being promoted by industry.

281. The official position of ACOG on pelvic floor mesh kits in February 2007 was that the procedures were 'experimental and patients should consent to surgery with that understanding.'

C. DR. ANNE WEBER STRESSES RISKS OF MESH FOR SUI AND POP, IMPORTANCE OF ADEQUATE PATIENT INFORMED CONSENT, INDUSTRY'S ROLE AND PHYSICIANS' NEED TO HAVE SUFFICIENT CLINICAL DATA BEFORE ADOPTING NEW PROCEDURES

282. Anne Weber, MD, was the Program Officer in the Female Pelvic Floor Disorders Program, Contraception and Reproductive Health Branch, Center for Population Research, National Institute of Child Health and Human Development, National Institutes of Health in Bethesda, MD. In an article published in 'OBG Management' in December 2006, [226] according to Dr. Weber, mesh erosion (or exposure, extrusion) for SUI sometimes is accompanied with infection. She continued about the new sling technology echoing the

[226] Weber AM. Urinary Incontinence OBG Management December 2006, p 45-52, www.obgmanagment.com

message of ACOG and Dr. Ostergard that sling procedure kits were 'experimental' based on a "lack of long-term clinical data":

> *Even worse, companies commonly withdraw products, modify them, and reintroduce them to the market, accompanied by intensive marketing but, as with the original product, without any real evidence of safety and effectiveness.*
>
> *In an ideal world, clinicians (and patients) would insist on evidence before accepting new products and techniques. Failing that, clinicians (and patients!) should clearly understand that all new products and techniques are experimental until they are proven equal of better than traditional techniques...*
>
> *Among the most important evidence on slings this year are reports of investigations that demonstrated what should not be done.*

283. In February 2009, Dr. Weber once again wrote an article published in 'OBG Management', now on the issue of urethral slings and the need for physicians to counsel patients on what can be considered "experimental" surgery. She began by stating that from her vantage point, it appeared that "economic factors were playing an increasingly important role in how pelvic organ prolapse (POP) and urinary incontinence (UI) are managed-particularly, in regard to the use of surgical devices." Dr. Weber indicated that she was not against innovation but that she was of the opinion that "innovation must be demonstrated to be an improvement before it is incorporated into practice." Regarding the current FDA clearance process (510(k)) that permitted these new mesh devices on the market without providing clinical data, she urged physicians that "it's our duty to insist on evidence of safety and effectiveness before adopting the latest and greatest products that companies have to offer." Dr. Weber addressed the issues of the ACOG Practice Bulletins and subsequent revision. In ACOG's Bulletin #79, February 2007 (original wording) :

> *Given the limited data and frequent changes in the marketed products (particularly with regard to the type of the mesh material itself, which is mostly associated with several of the postoperative risks especially mesh erosion),* ***if clinicians recommend these procedures before evidence of their risk-benefit is fully understood, the procedures should be considered experimental and patients consented for surgery with that understanding.***[227]

284. ACOG's subsequently revised ACOG Practice Bulletin #84 September 2007 eliminated the use of the word "*experimental*" but still continued to convey the message of the need for physicians to provide patients with adequate informed consent regarding the lack of long-term outcomes data (revised wording):

> *Given the limited data and frequent changes in the marketed products* ***for vaginal surgery for prolapse repair*** *(particularly with regard to the type of the mesh material itself, which is mostly associated with several of the postoperative risks especially mesh erosion),* ***patients should consent to surgery with the***

[227] Weber, AM, Are new tools for correcting prolapse and incontinence better just because they're new? OBG Management, February 2009, Vol. 21 (No. 2): (http://www.obgmanagment.com)

understanding of the post-operative risks and lack of long-term outcomes data.[228]

285. Dr. Weber continued to speculate as to the reason why ACOG changed its original wording in Practice Bulletin #79:

> *If we cannot always rely on industry to provide clear information about the risks and benefits of new devices, neither can we routinely look to professional organizations for unbiased information. Often, professional organizations accept cash contributions from industry, raising the question of conflict of interest that may undermine their actions when priorities of industry do not align with the goal of safeguarding patients' well-being.*
>
> *The deletion is crucial because offering informed consent for surgery requires a patient to accept risks in balance with expectation of benefit. A patient cannot be appropriately informed when no evidence of benefit exists and evidence of postoperative risk is extremely limited.*
>
> *Now, I am not declaring that ACOG acted out of bias because of a financial conflict of industry with industry in this instance; the fact that financial conflict of interest exists for ACOG, however, cannot be disputed if one examines the College's Annual Report, where contributors are listed...*[229]

286. Dr. Weber continued:

> *Am I anti-industry? Only when there is unbridled race to profit from marketing products without safeguards to ensure, first and foremost, the safety of our patients and , second, their long-term effectiveness...*
>
> *Prolapse and incontinence are deeply distressing for our patients, but these chronic conditions are not life-threatening; virtually all women who suffer these conditions have been symptomatic for years before they come for care. I see no need, except to increase the bottom line, to rush products to market before they have been evaluated sufficiently to determine whether "new" is actually "better".*[230]

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[228] Weber, AM, Are new tools for correcting prolapse and incontinence better just because they're new? OBG Management, February 2009, Vol. 21 (No. 2): (http://www.obgmanagment.com)

[229] *Id.*

[230] *Id.*

VIII. FDA INCREASES ITS ACTIVITIES TO PROTECT PATIENT SAFETY AND OVERSEE TRANSVAGINAL MESH PRODUCTS

A. FDA WARNED THE PUBLIC DIRECTLY VIA ITS PUBLIC HEALTH NOTIFICATION OF 2008 OF "SERIOUS COMPLICATIONS" ASSOCIATED WITH PLACEMENT OF SURGICAL MESH FOR PELVIC REPAIR OR SUI

287. FDA issued on October 20, 2008 "Public Health Notification: Serious Complications Associated with Transvaginal Placement of Surgical Mesh in Repair of Pelvic Organ Prolapse and Stress Urinary Incontinence."[231] The notification was to alert healthcare practitioners to complications associated with transvaginal placement of surgical mesh to treat pelvic organ prolapse (POP) and stress urinary incontinence (SUI). By 2008, FDA indicated it had had already received over the prior three years, greater than 1,000 reports of adverse events from nine surgical mesh manufacturers of complications associated with surgical mesh to treat POP and SUI.

288. FDA continued in the Alert by describing the complications and events with surgical mesh:

> *The most frequent complications included erosion through vaginal epithelium, infection, pain, urinary problems, and recurrence of prolapse and/or incontinence. There were also reports of bowel, bladder, and blood vessel perforation during insertion. In some cases, vaginal scarring and mesh erosion led to significant decrease in patient quality of life due to discomfort and pain, including dyspareunia.*
>
> *Treatment in the various types of complications included additional surgical procedures (some of them to remove the mesh), IV therapy, blood transfusions, and drainage of hematomas and abscesses. (FDA Public Health Notification October 20, 2008).*

289. There was no risk information in the FDA's 2008 Alert regarding the complications of Transvaginal mesh (TVM) Placement of Surgical Mesh in Repair of Pelvic Organ Prolapse and Stress Urinary Incontinence that had not been just as available to industry and Ethicon. At any time Ethicon could have voluntarily updated its TVT-SECUR product IFU with risk information and warnings, as well as its marketing and training materials and patient brochures prior to 2006 and again prior to 2008. There was no need for Ethicon to obtain FDA's approval to update (improve) its risks information and warnings for TVT-SECUR materials.

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[231] Public Health Notification: Serious Complications Associated with Transvaginal Placement of Surgical Mesh in Repair of Pelvic Organ Prolapse and Stress Urinary Incontinence, available at http://www.fda.gov/MedicalDevices/Safety/AlertsandNotices/PublicHealthNotifications/UCM061976 (last visited January 25, 2016).

B. FDA HELD A SEPTEMBER 2011 PUBLIC ADVISORY COMMITTEE (AdCom) PANEL MEETING TO DISCUSS RISKS OF UROGYNECOLOGIC SURGICAL MESH SLINGS

290. The FDA held a public advisory meeting of scientific experts (Obstetrics and Gynecology Devices Panel) on September 8-9, 2011 to assist the FDA with addressing the risks for women associated with surgical mesh slings used for treatment of SUI and POP. In preparation for the meeting, the FDA conducted its own review of the published scientific literature from 1996 to 2011 for surgical mesh slings used for SUI (and POP) as well as conducted a review of Medical Device Reports (MDRs) received from January 1, 2008 through September 30, 2011.[232]

291. Both the AdCom panel members and the FDA found that for SUI repair the medical literature had fewer long-term follow-up studies compared to studies published with only one-year follow-up data. Mesh slings for SUI repair were reported as successful in approximately 70 to 80% of women at one year, a similar effectiveness that was reported for non-mesh SUI surgeries. The safety and effectiveness of "mini-slings" like TVT-SECUR for treatment of female SUI had not been adequately demonstrated. Presently, it was unclear to FDA or the Panel how single incision (SIS) mini-slings like TVT-SECUR compared to implantation of multi-incision larger slings with respect to safety and effectiveness for treating SUI.

292. The use of traditional TVM slings in SUI repair, such as Ethicon's TVT and TVT-O Systems introduced a risk for women that had not been present in traditional non-mesh surgery for SUI repair. The new risk was the risk for mesh erosion, also known as mesh extrusion. Erosion of the mesh sling through the woman's vagina was the most commonly reported mesh-specific adverse event for SUI surgeries using mesh. According to the FDA in 2011, the average reported rate of mesh erosion at one year following SUI surgery with implanting mesh was approximately 2%. Some mesh erosion patients were able to be treated with application of vaginal cream and/or as an office procedure for trimming the exposed piece of mesh. However, treatment of some mesh erosions will require a patient to return to the OR to have a surgical procedure to remove all or part of the mesh and address complications.

293. The long-term complications reported in the medical literature were consistent with the events being described in FDA's MAUDE[233] database of MDRs. The complications associated with the use of surgical mesh slings currently marketed for SUI was not able to be linked by FDA to a single brand of mesh. In terms of safety conclusions by the FDA from its literature review which was focused on POP, more than half of the women who experienced erosion with a non-absorbable mesh required surgical excision in the operating room, with some requiring two or three additional surgeries.[234] New onset SUI has been reported to occur more frequently following mesh augmented anterior repair compared to

[232] Medical Devices Consideration about Surgical Mesh for SUI, available at (last visited January 25, 2016).
[233] MAUDE: Manufacturers and User Device Experience (MAUDE) database
[234] Abed, *et al.*, Incidence and Management of Graft Erosion, Wound Granulation, and Dyspareunia Following Vaginal Prolapse Repair with Graft Materials: A Systematic Review. Int Urogynecol J, 2011.

traditional anterior repair without mesh.[235] FDA would subsequently update its SUI risk information for patients and physicians in actions of 2012 and 2013. Again the risk for mini-slings like TVT-SECUR was unknown. The TVT-SECUR had been one of the initial mini sling implanted for SUI.

294. The FDA also conducted its own review of the MDRs received by the FDA from January 1, 2008 through September 30, 2011. The incidence of complications could not be estimated by use of FDA's received MDRs. There is acknowledged under-reporting of adverse events to the FDA as MDRs.

295. FDA's search of MDRs from January 1, 2005 through December 31, 2010 identified 3,979 reports of injury, death and malfunction. Among the 3,979 reports, 2,874 were received by FDA in the last 3 years (January 1, 2008 to December 31, 2010) and included 1,503 reports associated with POP repairs and 1,371 associated with SUI repairs. The number of MDRs associated with POP repairs increased by more than 5-fold compared to the number received in the previous 3 years (January 1, 2005 through December 31, 2007).

296. During the search timeframe, the FDA received 1,876 MDRs for complications associated with surgical mesh devices used to repair SUI. The most common reports in descending order of frequency, included: pain, mesh erosion through the vagina (also called exposure, extrusion or protrusion), infection, urinary problems, recurrent incontinence, pain during sexual intercourse, bleeding, organ perforation, neuro-mU.S.C.ular problems and vaginal scarring. With the exception of mesh erosion, the other complications could occur following a non-mesh surgical repair of SUI. Regarding the use of the FDA's MDRs, the FDA wrote:

> *While MDRs are a valuable source of information, this passive surveillance system has notable limitations, including the potential submission of incomplete or inaccurate data, under-reporting of events, lack of denominator data (number of implants), and lack of report timeliness.*[236]

C. FDA IN MARCH 2013 UPDATED ITS OWN UROGYNECOLOGIC SURGICAL MESH WEBSITE TO INCLUDE ADDITIONAL INFORMATION ABOUT RISKS OF MESH TREATMENT OF 'SUI'

297. FDA's Recommendations for Health Care Providers for SUI included being "vigilant for potential adverse events from the mesh sling, such as erosion." The physician was also told by FDA to "watch for complications associated with the use of the tools used in transvaginal placement of the mesh sling during the surgical procedure, such as bladder perforations." A patient was to be informed by her physician of her choice to have elective incontinence surgical repair with or without the use of a mesh sling. The patient should understand that "there is limited information about the outcomes after one year" and that the "mesh sling is a permanent implant." The physician was to "ensure that the patient understands the

[235] Altman D, *et al.*, Anterior Colporrhaphy versus Transvaginal Mesh for Pelvic-Organ Prolapse. NEJM 2011; 364:1826-36.

[236] Medical Devices Consideration about Surgical Mesh for SUI http://www.fda.gov/MedicalDevices/ProductsandMedicalProcedures/ImplantsandProsthetics.html

postoperative risks and potential complications of mesh sling surgery." Finally, the patient was to be provided with a "copy of the patient labeling or brochure, if available from the manufacturer."

D. FDA ISSUED AN ORDER CALLING FOR SECTION '522' POSTMARKET SURVEILLANCE STUDIES FOR UROGYNECOLOGIC MESH SLING SYSTEMS

298. Based on the FDA's AdCom Panel's deliberations, assessment of MDRs submitted to the FDA, and evaluation of the published literature, the FDA considered whether urogynecologic surgical mesh used for transvaginal repair of pelvic organ prolapse (POP) should be reclassified from Class II (low-to-moderate-risk devices) with clearance by 510(k) to Class III (high risk devices) requiring FDA's Premarket Approval. The Panel recommended to FDA that surgical mesh for SUI continue to remain at Class II (low-to-moderate-risk). In July 2013, both synthetic mesh for POP and SUI remain classified by FDA as class II and able to be cleared by 510(k). There was no specific recommendation for the mini slings like TVT-SECUR since the devices were considered too recently implanted when compared to the TVM SUI products such as TVT and TVT-O.

299. The Food and Drug Modernization Act of 1997 (FDAMA) modified post market surveillance (PS) requirements under section 522 of the Act. The Director of Office of Surveillance and Biometrics (OSB) will generally issue the orders for postmarket surveillance under section 522 (21 C.F.R.§ 822.7). Postmarket surveillance requirements under section 522 may be established for a device category, and the Office of Device Evaluation (ODE) may issue orders for section 522 studies as part of device approval or a substantial equivalence determination (clearance). Specifically, under the Act, the agency may:

> *...require a manufacturer to conduct postmarket surveillance for any device of the manufacturer which is a class II or class III device that the failure of which would be reasonably likely to have serious adverse health consequences or which is intended to be-*
> *(1) implanted in the human body for more than one year, or*
> *(2) a life sustaining or life supporting device sued outside a device user facility.*[237]

300. On January 13, 2012, the FDA ordered that postmarket surveillance studies ("522 studies") be conducted by manufacturers of urogynecologic surgical mesh devices, whether indicated as transvaginal mesh for POP or "mini-slings" for SUI repair to address specific safety and effectiveness concerns. This Agency order was based on the FDA's evaluation of the published literature, analysis of adverse events reported to the FDA and feedback from the Obstetrics and Gynecology Devices Panel of the Medical Device Advisory Committee. The order was also based on the FDA's authority to require postmarket surveillance studies (section 522).[238]

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[237] Guidance for Industry and FDA Staff Postmarket surveillance Under Section 522 of the Federal Food, Drug and Cosmetic Act issued on April 27, 2006.

[238] FDA Guidance for Industry and FDA Staff Postmarket Surveillance Under Section 522 of the Federal Food, Drug and Cosmetic Act issued April 27, 2006. The document supersedes FDA's "Guidance on Procedures to

301. As of February 17, 2013, the FDA issued 14 postmarket study orders for seven manufacturers of mini-slings for SUI. The FDA considers the specific adverse events for SUI and POP to be low-frequency but "life-altering" adverse events that can occur following both SUI and POP repair with surgical mesh.

302. FDA has established a 522 website that list the 522 commitment status of medical device manufacturers in terms of completion of 522 PS studies. The FDA on its TPLC website has classified FTL surgical mesh used a for a new device, sub-urethral "mini-sling" for treatment of SUI with the ProCode "PAH" to distinguish it from other mesh sling system used for repair SUI assigned OTN. The device is "Mesh, Surgical, Synthetic, Urogynecologic, For Stress Urinary Incontinence, Female, Mini-Sling."

303. The FDA's definition of the mesh sling for treatment of SUI remains the same as other SUI surgical mesh treatment:

> "*...transvaginal surgical repair of female stress urinary incontinence (SUI) due to intrinsic deficiency (ISD) and/or urethral hypermobility.*"

304. Technical method for the placement of a single incision mini-sling differs from the placement of other mesh sling systems for SUI:

> *With a single vaginal incision, the sling is placed under the urethra; during instances of increased abdominal pressure (e.g., coughing, laughing, sneezing, etc.) the device applies pressure to the urethra to prevent urine leakage.*

305. The device problems for PHA mini-slings for SUI have 23 problems listed with "No Known Device Problem" as #1 with 20 reports; "Break" as 2 reports; and "Other" as one report.

306. In 2013, there were thirteen (13) cleared 510(k)s for the surgical mesh mini-sling PAH for SUI. The FDA's first clearance of a PAH mini-sling application for Defendant was in 2005 (before the FDA's Public Health Notification). In January 2016 there are seventeen (17) 510(k)s listed as product code "PAH" for SIS mini sling. The earliest is Herniamesh T-Sling cleared May 15, 2002; followed by Gyne Ideas Mini Tape RP Device cleared June 18, 2003, the predicate for TVT-SECUR. Next is Ethicon's one and only cleared mini sling "GYNECARE TVT SECUR" K052401cleared on November 28, 2005. Despite the product having been de-commercialized, the cleared 510(k) will remain present on the FDA's website. The largest number of cleared 510(k)s for marketing of a mini sling belongs to American Medical Systems with 5 cleared devices.

Determine Application of Postmarket Surveillance Strategies" and "Guidance on Procedures for Review of Postmarket Surveillance Submissions" February 19, 1998 and "Guidance on Criteria and Approaches for Postmarket Surveillance" issued November 2, 1998. In 2006, the FDA consolidated the three prior 1998 guidances pertaining to postmarket surveillance into a single guidance. After 1998 when the three guidances were first issued, the FDA issued regulation to implement postmarket surveillance provisions of the Federal Food, Drug and Cosmetic Act, 21 U.S.C. § 360I.

E. FDA ISSUED ETHICON A 522 ORDER IN JANUARY 2012 REQUIRING IT TO OBTAIN POSTMARKET POST-MARKET PERFORMANCE INFORMATION FOR TVT-SECUR TO UPDATE THE RISK INFORMATION FOR PHYSICIANS AND PATIENTS

307. On January 3, 2012, the FDA issued a 522 Order[239] to Ethicon regarding the TVT-SECUR, mini-sling asking for postmarket surveillance studies. The FDA did not issue 522 Orders for SUI products TVT and TVT-O Systems. So in 2012, the FDA was clearly making a distinction in terms of risk information between the TVT kits and TVT-SECUR as a SIS mini sling and per the comments of its expert advisory panel.. The FDA determined that this Order was necessary to determine the safety and efficacy of the TVT-S for the treatment of SUI. FDA wrote to Ethicon that it was concerned with potential safety risks for GYNECARE TVT-SECUR as evidenced by the adverse events reported to the FDA and in the published literature.

308. In addition, the FDA was concerned with published literature indicating lack of added clinical benefit compared to non-mesh repair. Section 522 of the FD&C A, 21 U.S.C. § 360l authorized FDA to require a manufacturer to conduct postmarket surveillance of a class II or class III device. TVT-S as a class II device met two of the requirements for a 522:

> *Its failure would be reasonably likely to cause mesh erosion (i.e. organ perforation), severe pain, and fistula formation, which would meet the definition of "serious adverse health consequences" at 21 C.F.R. § 822.3(j). In addition, your device is intended to be implanted in the body for more than one year.*[240]

309. FDA recommended the use of a randomized clinical trial ("RCT") or prospective cohort study design that compares your device (s) to a control (e.g. transvaginal urogynecologic surgery without use of mesh) through 3 years of follow-up. In lieu of one of the study designs recommended above, FDA also permitted Ethicon to develop a new sponsor registry or RCT/cohort study nested within a registry to address the public health questions, either as a single institution or in collaboration with other sponsors. FDA indicated it was amendable to facilitating creation of a multi-sponsor registry to address these public health questions. Therefore, the FDA expressed its openness to discuss alternative methods for obtaining the post-market safety and efficacy information FDA wanted for these devices.

310. According to FDA, the clinical experience gathered from postmarket surveillance study may lead FDA to, among other things, recommending labeling changes regarding the use of your device. On April 29, 2014 the FDA issued two proposed orders for surgical mesh for TVM POP. Once final manufacturers will be required to provide clinical data in a premarket approval application (PMA) to support the safety and effectiveness of surgical mesh for POP. FDA also issued a proposed order to reclassify insertion instruments to class II with designation of special controls for Urogynecologic Surgical Mesh Instrumentation. On May

[239] ETH.MESH.04543027-ETH.MESH.04543030.
[240] ETH.MESH.04543027-ETH.MESH.04543030.

1, 2014 FDA issued "Effective Date of Requirement for Premarket Approval for Surgical mesh for Transvaginal Pelvic Organ Prolapse Repair" (21 C.F.R. §884.5980).

311. FDA told that Ethicon that it may want to consider the data requirements for a future PMA in deciding on the design of a 522 study for the TVT-SECUR. If approval of a PMA was a possibility for Ethicon for TVT-SECUR as a SIS mini sling, it should be indicated in the cover letter to FDA with Ethicon's submitted 522 study plan.

312. FDA concluded its 522 letter that:

> *Failure of a manufacturer to meet its obligations under section 522 is a prohibited act under section 21 U.S.C. 331(q)(1)(C). Further under 21 U.S.C. 352(t)(3) a device is misbranded if there is a failure or refusal to comply with any requirements under section 522 of the Act. Please note that violations of section 331(q)(1)(C) or 21 U.S.C. 352(t)(3) may lead to regulatory actions including seizure of the product, injunction, prosecution, or civil money penalties.*[241]

313. Ethicon subsequently sent a proposed postmarket surveillance plan to satisfy the 522 Order,[242] which was rejected in April 2012.[243]

314. In early May 2012, Ethicon sent notice to the FDA of its intent to de-commercialize the TVT-S and confirming that studies would not be required.[244] Ethicon requested that the Office of Surveillance and Biometrics place Ethicon's 522 orders be placed **on hold**. FDA was to communicate back confirmation of this plan to place the issue officially on hold. An internal May 13, 2012 email from Tim Schmidt to Chuck Austin. "Subject RE: Final Communication Package." The discussion in the email was about the confidential information to be distributed about Ethicon's decision to decommercialize PROLIFT, TVT-SECUR, and PROSIMA:

> *They [GYNECARE employees] will not be surprised by this decision but this will understandably fuel concerns regarding the attractiveness of the business and their role in the new world.*[245]

315. Ethicon's US Commercialization Decision was to provide a US Discussion Guide for Use with Customers (Implanting Surgeons) on May 15, 2010. The document was intended to provide support for how to handle fact-to-face meetings with ALL pelvic floor repair and incontinence surgeons (customers). The document identified the reason for discontinuation of the product as a "business decision."

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[241] ETH.MESH.03730582.
[242] ETH.MESH.04474731-ETH.MESH.04474740.
[243] ETH.MESH.04474782-ETH.MESH.04474785.
[244] ETH.MESH.04005095-ETH.MESH.04005096; *see also* Ron Horton deposition at 177:20-23 ("We opted not to go through with the 522 orders. We opted to suggest that we didn't want to go through with them.)
[245] ETH.MESH.04984186- ETH.MESH.04984188.

> *I also want to stress that this is not a recall, and not based on product safety. We stand behind the safety of our products. It is not necessary, based on this notification, for you to notify patients who have received these products, or for patients who have received these products to take any action.*[246]

316. The worldwide de-commercialization decision of TVT-SECUR was made in May 29, 2012, though notice was not sent to any doctors outside Ethicon.[247] When the ultimate decision to de-commercialize the product was made, Ethicon stated "[w]hile the TVT-SECUR product is associated with ***inferior patient-reported and objective cure rates*** at 1 year, and ***higher reoperation rates*** when compared to standard midurethral slings (e.g. TVT/TVT-O), Ethicon has concluded that the minimally-invasive procedure using TVT-SECUR is an acceptable choice of therapy ***for a carefully selected patient population*** when implanted by experienced surgeon."[248]

317. In addition, after the decision was made to decommercialize the TVT-SECUR, Ethicon and Johnson & Johnson formulated an extensive plan, under the leadership of Ron Horton, about what to tell the surgeons who were using the product: a so-called dos and don'ts guide.[249] Admittedly, Ethicon also informed the surgeons "not to tell women who they'd already implanted with the [product] that the company had decided to discontinue selling the product."[250] Ethicon justified this approach of not warning patients and surgeons about the risk of the TVT-SECUR based on maintaining that the product was safe and effective[251] even though the FDA experts determined that the products' safety and efficacy had not been established.[252]

IX. CONCLUSION

318. Based on my professional experience, knowledge, and training and my review, evaluation, integration, and synthesis of the information identified and discussed in this Report, including the materials and scientific/medical literature specified, it is my professional opinion, made to a reasonable degree of scientific and professional probability, that Ethicon and Johnson & Johnson did not comply with those duties required of a reasonably prudent medical device manufacturer with its development and marketing of TVT-SECUR in the United States.

319. Ethicon failed to evaluate the foreseeable risks and confirm the safety and effectiveness of the TVT-SECUR device in clinical trials prior to the commercial launch of these devices in the United States, despite the foreseeable risks of the device as a new SIS mini sling. The labeling for TVT-SECUR was inadequate and misleading and failed to warn physicians of the difficulties of the insertion for SUI, the difficulties experienced with the insertion tools and the significant learning curve seen in physicians already familiar with this type of

[246] ETH.MESH.05598522.
[247] ETH.MESH.05675500.
[248] ETH.MESH.05600916-ETH.MESH.05600923.
[249] Dep of Ron Horton 420:16-421:3.
[250] Dep. of Ron Horton at 429:14-25.
[251] Dep. of Ron Horton at 430:2-4.
[252] Dep. of Ron Horton at 430:5-7; *Id.* at 420:14.

surgery. The labeling was inadequate for multiple issues, including inadequate directions for use, beginning with the single incision size and depth, inadequate warnings and lack of adequate information about potentially serious, permanent and life-altering risks for the product when implanted for SUI. Ethicon failed to notify United States physicians and the FDA of its removal of the TVT-SECUR from Australia in 2007. Additionally, Ethicon did not adhere to its responsibilities for monitoring, complaint analysis, adverse event reporting, taking appropriate corrective and preventive actions to minimize risk and communication with physicians.